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SATURDAY MARCH 27 1954

TABLE OF CONTENTS

Results of Methonium Treatment of Hypertensive Patients F. H. SMIRK, M.D., F.R.C.P., F.R.A.C.P. 717

Oral Cortisone Treatment of Hypopituitarism
H. L. SHEEHAN, M.D., D.SC., F.R.C.P., F.R.C.O.G., and V. K. SUMMERS, M.D., M.R.C.P. 723

Analysis of 1,400 Cases of Acute Injury to the Head G. F. ROWBOTHAM, F.R.C.S., I. N. MACIVER, M.B., F.R.C.S.Ed., JUNE DICKSON, M.B., B.S., and MARJORIE E. BOURFIELD 726

Clinical and Experimental Study of Segmental Pain from the Shoulder N. W. NISBET, F.R.C.S.Ed. 730

Further Observations on the Metabolic Stimulating Effect of Salicylate
J. B. COCHRAN, M.B., F.R.F.P.S., M.R.C.P. 733

"Failed Forceps": A Review of 100 Cases R. LISLE GADD, M.B., M.R.C.O.G. 735

Crises in Congenital Spherocytic Anaemia (Acholuric Jaundice)
J. L. EMERY, M.D., D.C.H., and D. W. LEMMON, M.B., B.Chir. 737

Further Trial of Aureomycin in the Treatment of Cholera
S. C. SEAL, Ph.D., M.B., B.S., D.P.H., M. M. GHOSH, M.B., B.S., and S. C. GHOSAL, M.B., B.S., D.P.H., D.B. 740

MEDICAL MEMORANDUM

Spontaneous Perforation of Colon due to Alkaline Medication. ROGER BREARLEY, M.P., F.R.C.P. 743

BOOK REVIEWS 744

CLINICAL PATHOLOGY

Assessment of Adrenal Cortical Activity.
F. T. G. PRUNTY, M.D., F.R.C.P. 751

GENERAL ARTICLES AND NEWS

Paul Ehrlich and Emil von Behring 754
RECOGNITION OF INTOXICATION 753
MEDICO-LEGAL 766
MEDICAL NOTES IN PARLIAMENT 767
VITAL STATISTICS 768
MEDICAL NEWS 769
BIRTHS, MARRIAGES, AND DEATHS 771
QUESTIONS AND COMMENTS 771

OBITUARY

H. W. Marett Tims, O.B.E., M.D. 764
Ambrose Emerson, M.D. 764
Edgar Stevenson, M.D. 764
G. H. Grills, M.D. 764
C. B. Cohen, M.D. 765
U. W. N. Miles, M.R.C.S. 765
D. B. Kenny, M.B. 765
Dame Grace Kimmins, D.B.E. 765
J. B. Herrick, M.D. 765

LEADING ARTICLES

Good General Practice 746
Adolescence 748

ANNOTATIONS

Alcohol and Road Accidents 749
Antihaemophilic Globulin 750
New Fellows of Royal Society 750

CORRESPONDENCE

Ion-exchange Resins. M. L. ROSENHEIM, F.R.C.P. 758
Thrombo-embolism. L. POLLER, M.B. 758

SUPPLEMENT

Full Contents on First Page of Supplement
Annual Report of Council 83
Scottish News 125
Correspondence:
Hospital Staff Appointments. D. WILKIE, F.R.C.S. 127
Remuneration of Hospital Medical Staff. V. TORRY BAXTER, M.B.; M. P. COPLANS, M.B.; R. NORTON, M.B.; N. ROSS SMITH, F.R.C.S.; P. W. HOUGHTON, F.R.C.S. 127
Whole-time Specialist Appointments. H. JOULES, M.D. 129

CORRESPONDENCE—*cont.*

Anaesthesia in Breech Delivery. D. C. DRUITT, M.R.C.S. 758
Utero-tubal Insufflation. F. E. STABLER, F.R.C.S. 758
The Thyroid. T. LEVITT, F.R.C.S. 759
Caudal Analgesia. H. R. YOUNGMAN, M.D., F.F.A. R.C.S. 759
Hibernation Anaesthesia. A. SMITH, F.F.A. R.C.S., and J. G. FAIRER, D.A. 759
Methylpentynol. M. M. GLATT, M.D. 760
Peptic Ulcer. W. N. LEAK, M.D. 760
Slow Combustion Stoves. C. B. HEALD, M.D. 760
Gastro-intestinal Fuso-spirochaetosis. I. G. K. MENON, M.B. 761
Smoking and Mouth Cancer. P. WADE, M.B., D.M.R. 761
"Status Lymphaticus." W. G. WAUGH, F.R.C.S.Ed.; H. UCKO, M.D. 761
Medical Auxiliaries. S. M. EVANS, M.C.S.P. 762
Recruitment of Nurses. A. E. WILLSON-PEPPER, S.R.N., and J. K. WILLSON-PEPPER, F.R.C.S. 762
Child Health. J. H. THOMPSON, M.B. 762
Emotions and the Nose. C. C. HARVEY, M.D. 763
Herpes and Eczema. J. I. HOFMAN, M.D. 763
Burns and the Adrenal. H. F. WEST, M.D.; J. A. STRONG, M.R.C.P. 763
Thyrotoxicosis. D. K. O'DONOVAN, M.D. 763

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 27 1954

RESULTS OF METHONIUM TREATMENT OF HYPERTENSIVE PATIENTS*

BASED ON 250 CASES TREATED FOR PERIODS UP TO 3½ YEARS, INCLUDING 28 WITH MALIGNANT HYPERTENSION

BY

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Except in malignant hypertension, the outlook of the individual hypertensive patient treated only by rest, sedation, and the amelioration of complications is difficult to assess unless the prognosis has evidently deteriorated because of substantial cardiac failure or renal impairment.

Individual prognosis is hazardous, especially in milder cases, but the expectation of survival among large groups of hypertensive patients has been well worked out in terms of their presenting clinical features. Among such groups of patients the expectation of survival is related to the extent of hypertensive changes in the retina, the presence or absence of heart failure, cardiac asthma, breathlessness, substantial electrocardiographic changes and, in a general way, with the height of the blood pressure, especially the diastolic pressure. The age at which the patient begins to show such abnormal manifestations, and the sex, have a strong bearing on outlook. While different views are expressed, a scrutiny of the manner in which authors have gathered their clinical material, and of the age and sex of the patients, reveals that the divergencies are less than would appear at first sight. Differences in case selection, not always of an obvious kind, influence comparisons of the results of medical and surgical treatment.

In many publications on groups of patients submitted to sympathectomy, those who have impaired renal function, who have had heart failure or a previous stroke, or who are 60 years or more may be rejected. The selection may be such that the patients who are operated on have in any case a better outlook than the generality of cases, or a worse one if patients with malignant hypertension constitute a large proportion of the sympathectomy cases. It is important, therefore, to divide up hypertensive cases into a sufficient number of age groups and clinical categories, as these differ greatly in their outlook. Perhaps the clearest demonstration of the importance of subdividing the classes of hypertensives comes from Keith, Wagener, and Barker (1939), who showed the relationship between retinal changes and outlook in a series of hypertensive patients collected at the Mayo Clinic. Their series comprised 146 cases of malignant hypertension (grade IV), 37 of grade III, 26 of grade II, and only 10 of grade I. Possibly the preponderance of severe cases is related to the fact that patients are sent from a distance to the Mayo Clinic. My experience has been that cases referred from a distance are on average more severe.

The object of the present paper is to give an account of our experience with methonium treatment of hypertensive cases, mostly of substantial severity, over a period of three years and seven months. Over 250 patients have been treated. The effects of treatment upon the clinical manifestations secondary to hypertension have been of the same kind irrespective of the cause of high blood pressure. Later results confirm and to some degree improve on those published earlier (Restall and Smirk, 1950; Smirk and Alstad, 1951). This paper mainly concerns problems which could not be dealt with adequately at an earlier stage. Results in malignant hypertension (excluding nephritis) and in patients with hypertensive heart failure or cardiac asthma are given in detail. In the mortality studies on malignant hypertension we have reported on 28 patients, including all who died and all living patients on treatment for five months or more. In mortality studies on patients in grades III, II, and I, almost all the 142 patients have been on treatment for periods betwen one and three and a half years. For comparison there is a series of 71 untreated patients investigated by the same methods. These control cases were mainly patients who presented themselves for investigation and possible treatment on or after November, 1949, and were judged suitable for methonium treatment. They were not treated, either because of shortage of supplies or because they decided against treatment. On the whole these cases were somewhat milder than those treated.

It has become clear that there is a significant improvement in the life expectation of malignant hypertension cases. Other groups also show an improvement, but further observation will be needed before definite conclusions can be drawn.

*Communicated in part at a meeting of the British Medical Association (New Zealand Branch) in February, 1953, and in part as Wm. McIlrath Guest Professor, Royal Prince Alfred Hospital, Sydney, October, 1953.

Reports of clinical improvement with effective methonium treatment have been published by Rosenheim (1952), McMichael (1952), and Morrison (1953). There is general agreement concerning the character of clinical improvement when it occurs.

Method

The technique of treatment and the methods of determining the adequacy of control over blood-pressure levels have remained the same in principle but have improved in detail in the course of the past three and a half years. The methods used have been described elsewhere (Smirk, 1950, 1952b, 1952c ; Smirk and Alstad, 1951 ; Kilpatrick and Smirk, 1952). The method at present advocated has been described recently (Smirk, 1953a, 1953b). Greater detail is available in the latter paper.

1. Mortality Experience in Treated and Untreated Patients

Survival Times of Patients with Malignant Hypertension

All cases classified here as malignant hypertension have shown a clear-cut papilloedema, with some other retinal manifestations, such as circumpapillary oedema, hard and soft exudates, retinal haemorrhages, etc. In case of doubt the binocular ophthalmoscope was employed. No case diagnosed as malignant hypertension has been excluded from the series, but cases of nephritis are not included even though the fundal changes are of the grade IV type. Our malignant hypertension patients comprise 28 who have been on continuous treatment with methonium salts ; four others who were on treatment for a time and then stopped ; and 11 patients who were untreated, these having been seen mostly in the years before methonium treatment started. The results are set out in Tables I and II.

TABLE I.—*Mortality Experience in Malignant Hypertension*

Group A				Group B				Group C			
Died		Survived		Died		Survived		Died		Survived	
Case No.	M. S.	Case No.	M. S.	Case No.	M. S.	Case No.	M. S.	Case No.	M. S.	Case No.	M. S.
Treated with Methonium											
206	6	53	43		None	40	37	49	31	51	39
		54	39			204	24	52	15		
		41	37			207	23	76	10		
		123	33			220	24	227	2		
		124	32			306	14	337	4		
		161	28			357	9	E.8	1		
		216	23			361	11				
		336	12			364	9				
		371	7								
		382	8								
		400	5								
		E.7	21								
Controls Untreated											
L.C.	6	135	24	A.S.	1½		None	S.C.	½		None
		150	32*	P.R.	¼			R.G.	2		
				E.A.	4						
				F.M.	2						
				160	¼						
				A.H.	3						

M.S. = Months of survival. * Sympathectomy.

Of the treated patients seven died after periods of treatment lasting 10, 15, 31, 6, 2, 4, and 1 months. The clinical state and reaction to treatment of the patients who died are set out below:

Case E8 was admitted in a moribund condition. Case 227 was close to uraemia with repeated vomiting and high total N.P.N. He improved for a time, but died in three months from uraemia. Cases 76, 52, and 49 were admitted in advanced congestive failure with severe cardiac asthma. They improved for a time: Cases 76 and 52, up to the time of their deaths by cerebral haemorrhage, were active, able to climb stairs, and looked after their own homes. Case 49 recovered from heart failure and was able to climb stairs, but developed bilateral pneumonia, from which she died. She had poor renal concentrating capacity, and the underlying condition was partly responsible for a fatal outcome. Case 206 had extreme dryness of the mouth and loss of appetite under effective methonium treatment which had cleared his papilloedema. During attempts to modify and improve the regime he got out of control and developed acute pulmonary oedema, from which he died. Case 337 had advanced renal changes and died from intercurrent infection. Of the patients who were not treated, 9 out of the 11 were dead in six months ; two are alive, one at 24 months and one at 32 months, the latter having had a sympathectomy. The four additional patients who had a period of treatment and then stopped treatment had 3, 3, 17, and 7 months under methonium treatment and showed the usual degrees of clinical improvement while on treatment ; they survived periods of 3, 15, ¼, and 2 months without treatment before death occurred.

Of the 21 surviving patients, 15 are leading productive lives: 11 men are at work, and 4 women are doing housework. Two male patients are expected to return to work within a few weeks (Tables III and IV).

One female patient who managed her house and garden for 28 months became completely incapacitated by a hemiplegia during the last nine months.

Mortality Figures in Patients Who Could Have Been Considered for Surgical Treatment

A high proportion of our patients with malignant hypertension presented in a condition in which sympathectomy could not have been contemplated (group A on the classification of Keith, Woolf, and Gilchrist, 1949). There were others with disabilities which would not have altogether prevented sympathectomy—such as a previous major cerebral accident (two cases), an older age group than is ordinarily accepted (two cases), or a degree of cardiac failure or cardiac asthma (four cases) which, though it does not prevent sympathectomy in less serious cases, is associated with a worse prognosis in malignant hypertension (group B on the classification of Keith *et al.*, 1949). Seven patients presented with advanced cardiac or renal changes (group C).

When, however, we consider the results of adequate methonium treatment in patients who do not have any of the above-mentioned objections to sympathectomy, we find that up to the present only one patient out of a total of 13 has died. This patient lived for six months. The surviving patients in group A have lived for an average of 24 months. In a group of patients selected in a similar way by Keith *et al.* (1949) and treated by rest and sedation, five died at

TABLE II.—*Average Periods of Survival*

	Group A				Group B				Group C			
	Died		Survived		Died		Survived		Died		Survived	
	No.	M.S.	No.	M.S.	No.	M.S.	No.	M.S.	No.	M.S.	No.	M.S.
Treated with methonium ..	1	6	12	24	0		8	18·9	6	10·3	1	39
Controls (local)	1	6	2	28	6	1·87	0		2	1·25	0	
Controls (Keith *et al.* 1949)	5	13·3	4	26	8	1·8	2	9	4	1·3	0	

M.S. = Months of survival.

13.3 months and four survived for an average of 26 months. We had eight patients who came to us before methonium treatment was available and also three patients with malignant hypertension who refused treatment or came when supplies were insufficient. Of these 11 patients, nine died at an average of 1.8 months, and two, including a sympathectomy case, have survived for an average of 28 months after the first diagnosis of malignant hypertension was made.

TABLE III.—*Occupational State of Malignant Hypertension Patients Under Treatment*

Case No.	Sex	Additional Clinical Features Before Treatment	Age Starting Treatment	Occupation During Treatment	Months Survived on Treatment
		Leading a Productive Life			
41	M	—	48	Accountant	37
53	M	—	46	In general medical practice	43
123	M	—	56	Business executive	33
204	M	Left ventricular failure	45	Railway employee	24
207	M	" — "	57	Engineer—active	23
216	M		42	Sheep shearing, wool classing	23
336	M	Minor cerebral accident	47	Farmer	12
371	M	Encephalopathic attacks	46	Stokes furnace	7
382	M	" "	43	Garage work	8
400	M	Left ventricular failure	41	Priest—educational work	5
E7	M	—	45	Farmer	21
124	F	Subarachnoid haemorrhage	46	Housewife	32
161	F	2 minor cerebral accidents	32	"	28
220	F	Encephalopathic attacks	63	"	24
357	F	Left ventricular failure	52	"	9
		Partially or Potentially Productive			
51	M	Congestive failure. Low I.Q. Osteoarthritis	59	Worked 2 years on farm. Now in old men's home; sweeps and cleans up	39
306	M	Left ventricular failure. One leg amputated	55	Return to work expected soon	14
361	M	Cerebral accident before treatment. Recovering from aphasia	47	Physically fit. Return to work expected soon	11
		Leading a Productive Life up to Time of Death by Stroke			
52	F	Severe heart failure	47	Housewife	14
76	F	" "	43	"	10

TABLE IV.—*Occupational State of Malignant Hypertension Patients Under Treatment*

Case No.	Sex	Additional Clinical Features Before Treatment	Age Starting Treatment	Reason for Not Working	Months Survived on Treatment
		Incapacitated by Conditions Arising Before Treatment Started—Substantially Free from Original Hypertensive Symptoms			
364	M	Cerebral vascular accident	44	Stroke	9
		Incapacitated by Hypertensive Condition Developed During Treatment			
40	M	Heart failure	58	Well for 34 mths. Mental confusion 2 weeks	37
54	F	Severe encephalopathy	46	Ran her own house for 33 months, then incapacitated by severe stroke	39
		Much-improved Activity, But Remaining Semi-invalid up to Time of Death			
49	F	Severe heart failure and renal insufficiency	52	Lassitude	31
		Died in Hospital Without Making Substantial Improvement			
206	M	—	48	In hospital	6
227	M	Uraemia	44	" "	2
337	F	Diabetes. Kimmelstiel–Wilson disease	41	" "	4

Comparison of the Groups with the Series of Keith et al. (1939)

Our control series of untreated malignant hypertension cases is only 11 in number, but our experience has corresponded with that of Keith *et al.* (1939) in a much greater series. In the present series of untreated patients 18% were alive at 18 months; in the methonium-treated group 75% were alive at 18 months.

Comparing similar groups of patients with malignant hypertension, methonium treatment has been associated with extension of the survival period.

Survival Times of Patients with Essential Hypertension (Grades III, II, and I)

The grades of hypertension referred to above are those of Keith *et al.* (1939). Grade I cases show minimal or no retinal changes; grade II show distinct hypertensive changes in the retinal arteries, such as nipping of the arteriovenous crossings or waist-like narrowings of arteries, but no other changes; grade III show haemorrhages, hard or soft retinal exudates, retinal oedema, or some combination of these but without papilloedema. In certain cases retinal oedema encroaches on the disk edge and blurs its outline, but does not lead to actual elevation of the disk: such cases have been classified as grade III, the doubtful cases being examined for papilloedema by the binocular ophthalmoscope. Thirty-three patients and 15 controls were classified grade III; 89 treated patients and 38 controls were grade II; 20 treated patients and 7 controls were grade I. A total of 142 were treated (the great majority for 12 to 42 months). The 60 controls were collected over the same period of time.

The deaths are set out in Tables V and VI. With both treated and control patients it is evident that the mortality experience with grade III is less favourable than with grade II, and grade II less than grade I, in which latter there were no deaths in either the treated or the control series. The results of treatment in grade II may be approaching statistical significance, but the results in grade III as set out in Table V do not seem so promising. The number of patients in this group and the duration of experience are insufficient to justify any conclusion. It should be mentioned, however, that seven of the grade III cases were of much greater severity than any of the control series, and four of the deaths occurred in this group. Were these seven patients not counted, so making the treated and control

TABLE V.—*Mortality Experience With Hypertension of Grades III, II, and I*

Age	Grade III		Grade II		Grade I	
	Died	Survived	Died	Survived	Died	Survived
			Controls			
70+ ..	0	0	1	0	0	0
60–69 ..	1	2	4	5	0	0
50–59 ..	2	3	1	11	0	2
40–49 ..	2	5	4	11	0	3
30–39 ..	0	0	0	1	0	1
20–29 ..	0	0	0	0	0	1
Total ..	5 (33%)	10	10 (26·3%)	28	0	7
			Treated			
70+ ..	2	0	0	4	0	0
60–69 ..	1	2	1	14	0	1
50–59 ..	2	10	7	28	0	4
40–49 ..	3	7	3	25	0	8
30–39 ..	0	4	0	6	0	6
20–29 ..	1	1	0	1	0	1
Total ..	9 (27·3%)	24	11 (12·3%)	78	0	20

TABLE VI.—*Mortality Experience Grades III and II Combined*

	Died	Survived	Total
Controls ..	15 (28·2%)	38 (71·8%)	53 (100%)
Treated ..	20 (16·4%)	102 (83·6%)	122 (100%)

series more comparable, the difference in mortality would still not be great—33% deaths among controls and 22% among treated patients.

When grades II and III are considered together the mortality difference shows that more experience is needed before a definite pronouncement can be made. The obvious betterment in health and the statistical significance of the results in malignant hypertension give grounds for hope that the figures may be improved by the use of more effective methods of obtaining control over blood-pressure levels—as, for example, by the use of M. & B. 2050A orally or in a solution of polyvinylpyrrolidone for subcutaneous injection (Smirk, 1952a, 1953a, 1953b).

2. Changes in the Physical State of Patients with Malignant and other Forms of Hypertension

Effect of Control of Blood-pressure Level on Retina in Malignant Hypertension

Papilloedema cleared in 21 out of 23 patients who were on effective treatment for five months or more; the two who have not cleared at five and six months are much improved and look like doing so. Eight other patients showed improvement, but papilloedema was still perceptible at the last observation made. These include patients who did not maintain treatment (two cases) or went off treatment (two cases) or died within six months (three cases with renal insufficiency). The remaining patient has been on treatment about three months. In most instances disappearance of papilloedema takes three to four months, sometimes six months, of intensive treatment; and a reduction of blood pressure to normal or near normal levels at the trough of the fall is necessary. With the better control obtained latterly, it has been our experience that papilloedema can be dispersed in almost all instances and that failure to do so after four months' treatment is usually an indication that the blood-pressure reduction is insufficient in degree and duration. A clear reduction in the amount of papilloedema should be evident in three to four weeks, with reappearance of a physiological cup or of a part of the disk edge. The last residues of oedema take longest to disperse. It often happens that one disk is entirely clear of papilloedema and the other has lagged behind in improvement.

Within the first month of effective treatment soft exudates should have disappeared, there should be no fresh haemorrhages, and as a rule old haemorrhages have been dispersed. Hard exudate at this stage usually stands out shiny and with sharp edges. With effective treatment the hard exudate begins to soften at the edges and loses some of its shiny clear-cut delineation, looking more like soft exudate in some instances. Substantial dispersal of hard exudate is unlikely under six months and some may remain after 12 months, but it will be absorbed in most patients who have been under effective treatment for 12 to 18 months. In a few instances the edge of the disk will remain a little fuzzy as the result of post-papilloedema changes.

Examinations of such patients with the binocular ophthalmoscope have been made in most cases by Dr. Rowland Wilson in order to be sure that this was not residual papilloedema. New blood vessels round the edge and sometimes on the disk are a common residual finding after the papilloedema. In some instances the disk is pale, suggesting a minor grade of optic atrophy even though vision is good. The generalized vasospasm of so many patients with malignant hypertension tends to disappear and the general calibre of the arteries returns almost to a normal level. Such arterial changes as nipping of the arteriovenous crossings and waist-like narrowings in the course of arteries remain behind, but I am unable at this stage to comment on the question of whether any recession in such changes occurs or not.

At an early stage of our work a few patients with malignant hypertension were treated by continuous subcutaneous administration of hexamethonium bromide over a period of approximately 12 days, using an electrically operated power-driven syringe (Smirk, 1951). By this means the blood pressure was kept only a little above the normal level day and night. Papilloedema then seemed to clear much more rapidly than with intermittent blood-pressure falls from thrice-daily injections of aqueous hexamethonium bromide. Preparations have been devised which are absorbed more slowly owing to admixture with polyvinylpyrrolidone or dextran. The most satisfactory of these is the longer-acting methonium compound M. & B. 2050A dissolved in 20% aqueous polyvinylpyrrolidone, ephedrine hydrochloride being added to 1 in 200 concentration in order to prolong absorption by local vasoconstriction. With two, or at times three, injections daily of this preparation it has been possible to obtain a much better control than with three injections daily of aqueous hexamethonium bromide. In most instances oral administration of M. & B. 2050A is equally satisfactory. Under these conditions, apparently related to the better control over blood-pressure levels, dispersal of papilloedema and of other retinal manifestations seems to be accelerated.

Effect of Control of Blood-pressure Level on Retina in Patients with Grade III Changes

The appearance in these patients is similar to that in malignant hypertension except that there is no elevation of the optic disk. The disappearance of retinal haemorrhages, soft exudate, retinal oedema, and finally of hard exudate takes place in much the same way as in malignant hypertension.

Effect of Control of Blood-pressure Level in Heart Failure, Cardiac Asthma, and Simple Breathlessness

Hypertensive congestive heart failure or cardiac asthma was relieved by methonium therapy without the use of digitalis, mersalyl, or salt-free diet in 20 of the 36 cases. In most instances patients returned to the degree of activity appropriate to their time of life. Of the remaining 16 cases, seven required digitalis or mersalyl initially; but later, when methonium therapy was well-established, digitalis and mersalyl were withdrawn without recurrence of failure. In one patient who went into heart failure while on digitalis the failure was controlled by blood-pressure reduction; digitalis was omitted, but it was not possible to manage without a salt-free diet. In five other patients who went into failure while on digitalis (ages 51, 71, 70, 60, and 80) the breathlessness was considerably lessened, but remained an important disability and the digitalis could not be withdrawn. In three patients there was deterioration. In one we had been unable to establish an effective regime because of side-effects; in another case necropsy revealed that an extensive left ventricular infarction had maintained heart failure; in another uraemia and left heart failure were associated.

Of 27 patients under 60 years, six did not work, 11 men returned to gainful employment (one died later from a stroke), and 10 women were engaged in housework (two died later from a stroke).

With a few exceptions it has been possible to remove cardiac asthma and congestive heart failure and to render breathlessness unimportant without recourse to digitalis, mersalyl, or salt-free diet, except that a regime of "no added salt except in cooking" is sometimes advised. In a few instances where digitalis was in use before the patient came into hospital the dose was maintained at the level on which the manifestations of congestive failure had developed.

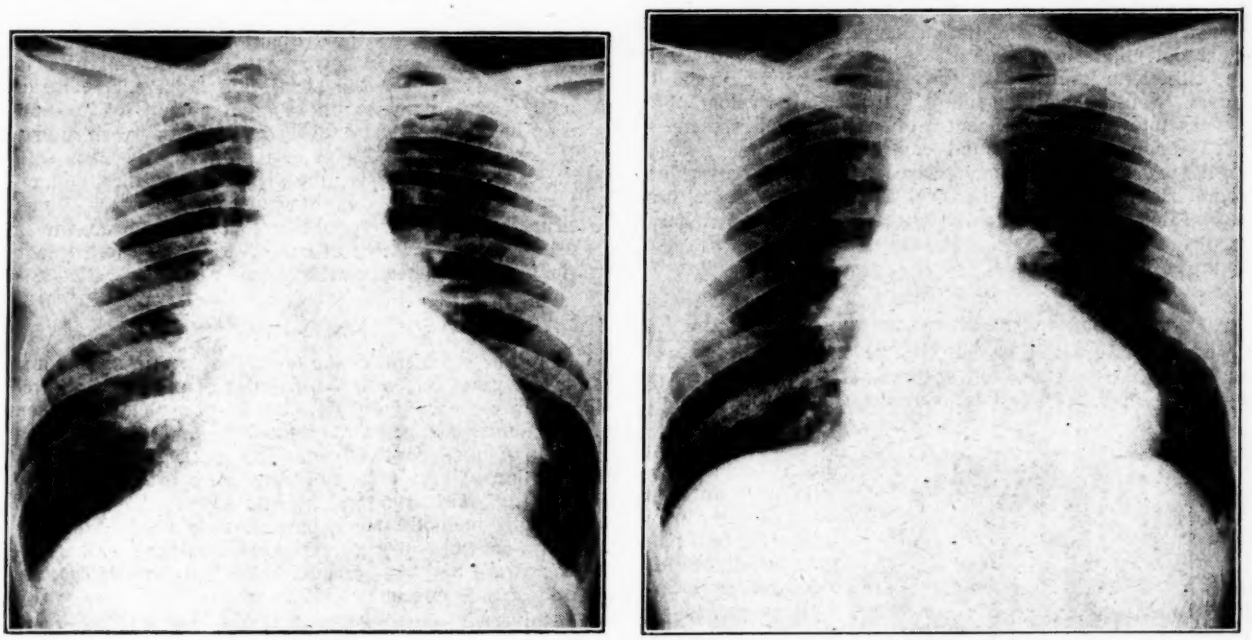
Attacks of cardiac asthma can be cut short by the administration of an appropriate dose of hexamethonium bromide or one of the other effective methonium salts, the patient being propped up in the sitting posture. If by fractional administration the blood pressure is reduced to as near normal as the patient will tolerate, a great degree of relief from breathlessness is commonly encountered as the blood pressure falls, even in cases of severe cardiac asthma. Fractional administration is advised because, were the dose given an excessive one, the normal counter-measure of

lowering the patient to the horizontal position in order to re-elevate the blood pressure could scarcely be applied if there was considerable orthopnoea.

It is a considerable advantage to heart-failure patients if the use of digitalis, mersalyl, or salt-free diets can be avoided because in most cases heart failure due to hypertension can be relieved without these measures. Recurrence of breathlessness provides a very useful warning that the degree of control over blood-pressure levels is insufficient. Sometimes, however, it is not possible to dispense with additional measures at the outset. It is better then to supplement methonium treatment by occasional injections of mersalyl, since when these are omitted it will soon be discovered whether the regime has allowed a sufficient recovery of the cardiac muscle. In about one in four cases, and especially in the elderly, a digitalis regime may be required as well as blood-pressure control.

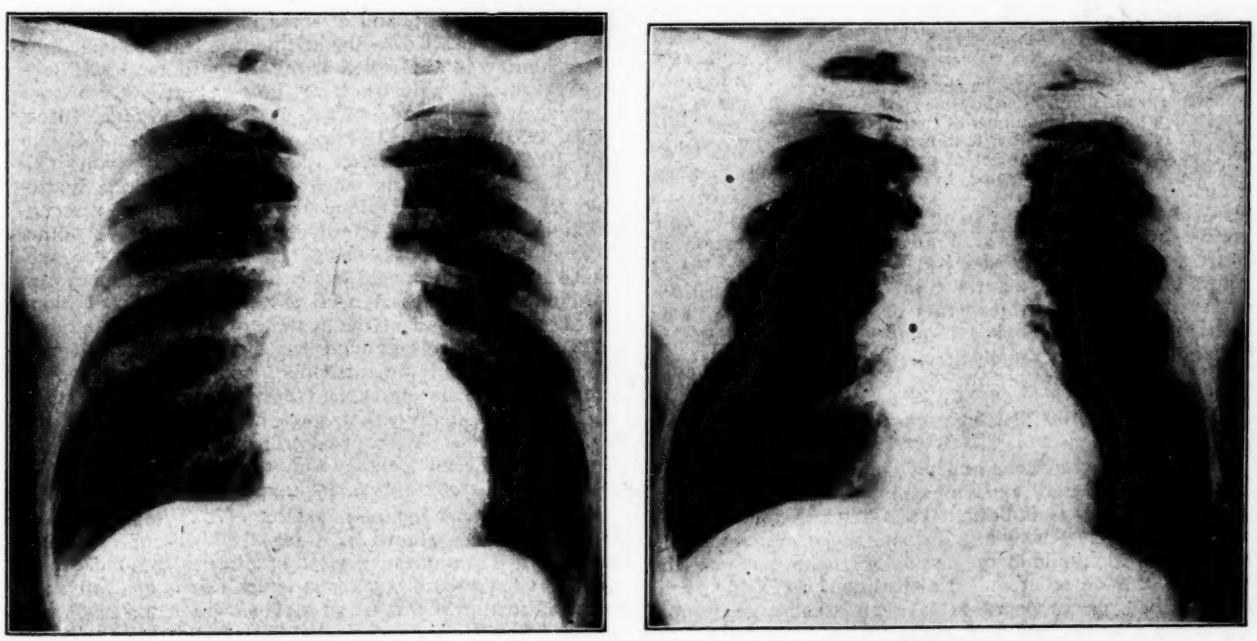
Effect of Control of Blood-pressure Level on the Electrocardiogram

Reference was made in an earlier publication (Smirk and Alstad, 1951) to improvement in the electrocardiogram



Before After

FIG. 1.—Case 204, male aged 45. The *x*-ray film prior to treatment was taken August 28, 1951, and corresponded with mild congestive heart failure and attacks of cardiac asthma. These cleared on methonium treatment without other measures. The patient returned to work. Second film was taken May 4, 1953.



Before After

FIG. 2.—Case 14, male aged 46. Before treatment there was mild breathlessness but no congestive failure or cardiac asthma. The first *x*-ray film was taken on January 27, 1950. Breathlessness cleared on methonium treatment. The second film was taken on June 12, 1953.

following effective blood-pressure reduction. These changes did not take place at once in response to the lower blood pressure, but were progressive over a period of up to a year or more. The results in our series of cases have been analysed since by Doyle (1953), and his report on hypertensive patients in general applies equally to malignant hypertension cases. With effective blood-pressure reduction of sufficient duration, the voltage of the R and S waves is decreased; the depressed ST segments in leads reflecting left ventricular potentials ordinarily return to the isoelectric level; inverted T waves in the left ventricular leads either become less inverted or become positive; raised ST segments and over-average T waves in leads reflecting right ventricular potentials and the cavity side of the left ventricular potentials show a return of the ST segment towards the isoelectric level and a decrease in the height of the T waves. A useful working rule is that if electrocardiographic defects show no improvement within a few months there is need for a more substantial control over blood-pressure levels. At a later stage any relapse of electrocardiographic signs has the same significance. Necropsy evidence has shown that, at least in some instances, gross muscular hypertrophy remains even though the electrocardiogram has returned almost to normal.

Effect of Control of Blood-pressure Level on Heart Size

It has been reported already that an unequivocal decrease in heart size is encountered not only in patients who have had congestive heart failure but in a small proportion of patients who have not had heart failure. Taking patients who have not had heart failure, there appears to be a general trend towards decrease in heart size as judged by measurement of the cardiac silhouette, though most of the individual changes in heart size lie within the possible range of variation for repeated *x*-ray pictures on the same individual. Fig. 1 shows an example of the effect on heart size of hexamethonium bromide in a patient with congestive heart failure; Fig. 2 an example of decrease in heart size in a patient who had no heart failure. Fig. 3 shows the changes of heart size in 76 patients after periods of several months to three years on treatment. It will be seen that when the change is outside the usual limits of variation it is more usually in the direction of decrease.

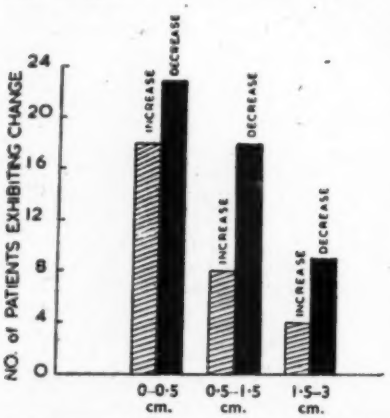


FIG. 3.—The figure surveys the changes in transverse heart diameter following methonium treatment. The number of patients with increase of diameter is shown by hatched columns; the number of patients showing decrease is denoted by black columns.

Effect of Control of Blood-pressure Level on Headache and Giddiness

The effect on headache and giddiness was referred to in earlier papers (Restall and Smirk, 1950; Smirk and Alstad, 1951), where it was indicated that failure to relieve headache and giddiness with an adequate regime was most exceptional. In preliminary discussions with patients the prospect of such relief may be mentioned as highly probable if they are prepared to take an amount of trouble comparable to that of a diabetic patient on insulin. In order to obtain such results the regime must be adjusted in terms of the reaction of the individual patient to the hypotensive agent. Thus, three adequate injections daily of hexamethonium bromide subcutaneously with adoption of the sitting posture throughout the night (body inclined at 45 degrees from the horizontal) commonly relieves headache. Some patients, however, still have morning headaches on this regime. The administration of an extra dose of hexamethonium bromide before retiring or the administration of an appropriate number—say 1 to 4—tablets of hexamethonium bitartrate with a little food to prolong the absorption will often, when combined with the sitting posture, prevent the development of headache the next morning. The administration of hexamethonium bromide in 20% polyvinylpyrrolidone proved more effective than the simple aqueous solution.

Latterly a further advantage has been obtained by the use of M. & B. 2050A in polyvinylpyrrolidone with 1 in 200 ephedrine hydrochloride incorporated in the mixture in order to delay further the absorption from subcutaneous tissues. A suitable injection at night commonly prevents morning headache. Alternatively or additionally an appropriate dose of M. & B. 2050A by mouth, usually taken with a little food so as to delay the absorption further, will relieve morning headache. From what has been said it should be clear that, in order to obtain relief from headache in almost all cases, a number of clinical trials have to be made and individual regimes devised to suit particular patients.

Discussion

Our results represent, at the most, the experience of three and a half years, and with the majority of patients a shorter time; but, even so, if our data be accepted there has been a fundamental change in the immediate outlook as regards survival of malignant hypertension patients as well as amelioration of symptoms and signs as reported previously (Restall and Smirk, 1950; Smirk and Alstad, 1951). This is achieved by methods which unfortunately need scrupulous long-term control and great expenditure of time, and which in general are not, but sometimes are, hard on the patient because of side effects.

The object of treatment is to reduce the blood pressure to near normal levels for as much as possible of the 24-hour day. A few patients have been treated by hexamethonium bitartrate by mouth, others by three daily injections of appropriate doses of aqueous hexamethonium bromide. Later the hexamethonium bromide was dissolved in 20% or 25% polyvinylpyrrolidone in order to prolong the period of absorption, and in some instances a further prolongation was effected by the addition of 1 in 200 ephedrine hydrochloride to the injection mixture. In the last fifteen months several patients have been treated by a new methonium compound, M. & B. 2050A (Smirk, 1952a, 1953a, 1953b; Wien and Mason, 1953; Maxwell and Campbell, 1953). This substance, dissolved in 20% polyvinylpyrrolidone, particularly when 1 in 200 ephedrine hydrochloride is added to prolong absorption by local vasoconstriction, acts more effectively than some 12 other methonium compounds which we have tested. The substance has the advantage that it may be administered also by mouth in most cases, with effective reduction of blood pressure. The detail of the method of controlling the dose of a methonium compound has been simplified (Smirk, 1953a, 1953b), but the method of control here advocated does not differ in principle from the more cumbersome methods used at an earlier stage in the treatment of this series of patients. Without control over the blood-pressure level of sufficient degree and duration the results of methonium therapy are most disappointing.

Common errors include: neglect of day and night control of posture; control of dosage in terms of occasional casual blood pressures; neglect of drug toleration; use of oral hexamethonium in cases in which this is ineffective; in injection treatment the use of syringes graduated in 0.2 ml. instead of 0.01 ml.; and the absence of effective instruction to patients with a written account of their regime.

In our patients, blood pressures are measured by technicians throughout six or seven hours of the day at approximately half-hourly intervals for five or six days of the week

and for three weeks. During this period each dose is adjusted in terms of response to previous doses—a kind of biological assay. The patient thereby gains a considerable insight into the principles underlying treatment. After the initial three weeks the patient attends the hypertensive clinic—weekly at first and later at longer intervals. Occasional all-day tests are made, but most of the control at this stage is in terms of *hypo*tensive symptoms. Casual blood pressures are taken, but they are of very little use in the control of dosage. Quite high blood pressures may be encountered in out-patients whose blood pressure, with methonium, is satisfactory under home conditions.

Summary

On three and a half year's experience it appears already that the prognosis of malignant hypertension is much improved by effective control over the blood-pressure level by the administration of methonium salts.

The result of treating all of 28 malignant hypertensive patients, including seven with substantial renal insufficiency or advanced heart failure, is that 21 are living and seven dead. The average survival time of those who died is 9.7 months and of those who are still alive 22.8 months. A considerable majority of the survivors are leading productive lives, the men working at their previous occupations and the women doing housework.

In hypertensive patients with retinal grades II and III, taken together, the mortality figures are better in 122 treated cases (16.4%) than in 53 controls (28.2%), but no claim of statistical significance is made.

Objective improvements include: (*a*) the disappearance in most cases of such changes as papill-oedema, retinal oedema, soft exudates, haemorrhages, and, after long treatment, of star-shaped macular figures; (*b*) the return to work of most patients under 60 presenting with malignant hypertension, cardiac asthma, or congestive heart failure, including in most instances the elimination of the use of digitalis, mersalyl, or substantial salt restriction; and (*c*) the electrocardiographic improvement and tendency to decrease of heart size. The consistency with which these results have been reproduced during three and a half years leads me to state that less satisfactory degrees of improvement are usually due to inadequacy of the regime used.

In a minority of patients the doses of methonium salts which relieve hypertensive manifestations lead to much discomfort from side-effects. Methods of alleviation which have helped some cases are suggested.

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ORAL CORTISONE TREATMENT OF HYPOPITUITARISM

BY

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In early trials of the therapeutic value of cortisone in hypopituitarism, the hormone was given in large dosage (75 to 100 mg. daily) for periods of about one to three weeks. The results were encouraging, but in some ways not satisfactory (Summers and Sheehan, 1951). Other workers using this dosage observed no beneficial effects (Robertson and Kirkpatrick, 1951; Brown and Greenblatt, 1952). Since then, a much lower dosage of cortisone has been tried for the continued treatment of these patients. Originally the cortisone was given either by injection or by implantation of pellets, but more recently oral therapy has been found just as efficient and far more convenient. Reports of single cases treated for long periods with doses of 12.5 to 25 mg. daily have been published by Thorn *et al.* (1950, 1951), Clark *et al.* (1951), Levy (1952), Perkins and Rynearson (1952), Roberts *et al.* (1952), McCullagh and Schaffenburg (1953), Tardy (1953), Dontigny (1953), Mathisen (1953), and Fourman and Horler (1954). More recently, a series of three cases treated in this way have been recorded by Hart (1953), and two cases by McCullagh *et al.* (1954). All these workers have reported good results from prolonged therapy at low dosage.

A few investigations have been made of the therapeutic value of cortisone in the treatment or prophylaxis of hypopituitary coma (Allott and Simmons, 1951; Sheehan and Summers, 1952; Paniagua *et al.*, 1952; Caughey *et al.*, 1952; Hijmans, 1952; Heyde, 1953). In addition there have been several reported studies of the effects of cortisone administered for very short periods for diagnostic tests or physiological studies, but these are not of direct relevance to the subject under consideration here.

Treatment of Present Cases

The following account concerns four patients with severe hypopituitarism who have been given small doses of cortisone orally over periods of about two years. Three of these were typical examples of severe hypopituitarism due to post-partum necrosis; the fourth was a man with hypopituitarism of unknown aetiology, probably due to some form of atrophy and scarring of the pituitary.

The patients were studied for a preliminary observation period of two to three weeks without treatment, and for a further control period of five weeks, during which 3 gr. (0.2 g.) of thyroid siccum was given daily. No significant effect was noted from the administration of thyroid. (This point merits a short interpolation. The warnings given in almost all textbooks about the dangers of thyroid therapy in patients with hypopituitarism appear to be overstated. Most of these patients tolerate ordinary dosage of thyroid without any recognizable ill effect. From a study of the occasional cases reported in the literature where the administration of thyroid was followed rapidly by coma, it seems probable that the patients were already on the point of developing coma in any event. Nevertheless, when

thyroid treatment is given, reasonable care should be taken. If the dosage is raised too much because of the lack of response, gastro-intestinal upsets and loss of weight can be produced; these two effects are serious in any patient suffering from hypopituitarism.)

After these periods of preliminary study, cortisone was given orally as "cortone" without any other treatment. The initial dosage was 12.5 mg. daily for one to two weeks, followed by 25 mg. daily for two to four weeks. In one patient it was increased to 37.5 mg. for two weeks and to 50 mg. for one week. Subsequently the amount was gradually reduced in all cases to 12.5 mg. daily as a maintenance dose. When the dosage was raised to 25 mg. one of the patients began to complain of insomnia. Another patient slept satisfactorily with this amount but had insomnia when the dose was increased to 37.5 mg. daily; she recovered when it was reduced to 25 mg. again. In all subsequent treatment the dosage was maintained at a level low enough to allow normal sleep.

Clinical Effects of Treatment

In all four cases there was a marked improvement in the general condition within three or four days. The patients became mentally alert and took a normal interest in their surroundings. They had an obvious sensation of well-being, became physically energetic, and were no longer sensitive to cold. Thus they were able to resume all their ordinary activities in the home and outside. The improvement was maintained satisfactorily on a daily dose of 12.5 mg.

The initial period of treatment with 25 mg. produced in all cases a normal capillary flush of the cheeks, a return of axillary secretion, and the occurrence of sweating on exercise. This improvement, once established, was maintained by 12.5 mg. daily. No changes developed in the face or elsewhere suggestive of a Cushing syndrome, even after two years' treatment. An experimental increase of the dosage to 50 mg. daily in one patient caused excessive perspiration.

Two of the female patients had no change in body hair, but the third female patient developed a small amount of pubic hair and some thickening of the head hair after six months' treatment. The male patient, in the course of six months' treatment, developed a slight amount of pubic hair and a slight return of hair on the legs; his beard became stronger, so that he needed to shave daily instead of once or twice a week.

The amenorrhoea was not affected in any way. No exact details are available about the libido of the female patients, but there was a return of a normal degree of pudor. Striking changes were, however, observed in the male patient, who for the previous five years had been completely without libido and had had no erections or other evidence of sexual activity. During the first three weeks of treatment with 12.5 mg. and 25 mg. of cortisone daily there was no obvious change. When he was given 37.5 mg. daily he began to have erections two or three times a week. After discharge from hospital on a maintenance dose of 25 mg. daily he continued to have frequent erections and had coitus two or three times a month, although no emissions occurred.

In two patients the blood pressure remained unchanged, the levels before treatment having been 130/80 and 140/90. In the third patient there was a slight rise, from 125/75 before to 140/75 during treatment. The fourth patient developed an irregularly increasing hypertension. The blood pressure was 130/80 previously and rose slowly during the first year of treatment to levels fluctuating between 150/90 and 180/130; subsequently it gradually returned to its original level.

Two of the patients had a definite increase in weight during several months' treatment; one rose from 104 to 135 lb. (47.2 to 61.2 kg.), and the other from 107 to 130 lb. (48.5 to 59 kg.). The third patient had a slight weight gain, rising from 92 to 96 lb. (41.7 to 43.5 kg.). The fourth patient lost weight during the thyroid treatment, falling from 162 to 151 lb. (73.5 to 68.5 kg.); on cortisone treatment she gradually regained this lost weight, and remained at 160 to 165 lb. (72.6 to 74.8 kg.).

Biochemical Changes

With these small and slowly increasing doses of cortisone there was none of the gross polyuria which follows immediately after parenteral treatment with high dosage. Nevertheless the urine volume slowly increased. Three of the patients had the following mean urine outputs before treatment and while on maintenance dosage respectively: (*a*) 1,120 and 1,680 ml., (*b*) 1,150 and 1,730 ml., and (*c*) 1,100 and 1,900 ml.

Kepler water diuresis tests were made on two of the patients. One whose maximum diuresis on the morning of the test had been 30 ml. an hour before treatment had a maximum of 140 ml. after treatment. The other had a previous maximum hourly excretion of 100 ml.; this increased during treatment to 165 ml. an hour.

It is well known that there is a great increase of nitrogen excretion in the urine when large doses of cortisone are given. This did not occur in the present series with low dosage. In one case the daily output of urea was unaffected by the treatment; in another there was a slight fall in the output of urea and creatinine, possibly in relation to nitrogen storage in the muscles.

There was always an increased output of 17-ketosteroids in the urine. Before treatment the output in the four patients had ranged between 0.2 and 1 mg. a day. On the maintenance doses of 12.5 to 25 mg. daily the urinary excretion of 17-ketosteroids ranged between 2.1 and 2.8 mg. a day. The increased output of 17-ketosteroids expressed in mg. daily corresponds to about 6% of the daily dosage of cortisone.

No significant changes were observed in the serum chemistry. The serum sodium remained at about the low range usual in these patients (280 to 300 mg. per 100 ml.) and the serum potassium fluctuated between 17 and 20 mg. per 100 ml. The serum cholesterol showed the usual wide fluctuations between 105 and 355 mg. per 100 ml., without any recognizable effect of treatment. The blood urea was rather high (commonly about 35 to 65 mg. per 100 ml.), but again there was no constant change related to the administration of cortisone.

There was no very significant alteration in the sensitivity to insulin, but the patients commonly showed some improvement in their response to hypoglycaemia. Several insulin-tolerance tests (using 0.03 unit per kg.) were performed in three of the patients; the mean blood sugars, expressed in mg. per 100 ml., were as follows:

Patient	Minutes:	0	20	40	60	120
A	Before treatment	72	52	37	40	42
	During "	77	49	49	54	66
B	Before "	95	67	50	63	65
	During "	96	61	63	73	74
C	Before "	102	57	66	73	88
	During "	86	63	64	68	81

The basal metabolic rate was studied in detail in only one patient. It had been −20% before treatment and continued in the range of −20% to −30% during cortisone treatment.

There was a definite though variable improvement in the anaemia. One patient with R.B.C. 4,100,000 and Hb 80% improved gradually to R.B.C. 4,700,000 and Hb 93%. The second patient, with R.B.C. 3,400,000 and Hb 70%, rose to an average of R.B.C. 4,200,000 and Hb 82%. The third patient with R.B.C. 4,000,000 and Hb 72%, rose to R.B.C. 5,000,000 and Hb 100%.

Effect of Cessation of Treatment

In three of the patients the cortisone therapy was stopped for a period of three months after about nine months' treatment. This produced a gradual but progressive deterioration in the

clinical state, so that at the end of a month they were almost back to the same condition as before treatment. They complained of marked asthenia, lack of perspiration, sensitivity to cold, and low urine output. The female patient who had had some return of pubic hair and thickening of head hair during treatment showed considerable regression of this hair growth after cessation of the cortisone. The male patient noticed that he required to shave very much less often, and his libido and erections had disappeared entirely within about two months. Two of the patients began to complain of rheumatic pains in the knees and ankles about two months after stopping treatment, though there were no recognizable physical changes in the joints.

After the three months without cortisone these three patients were put back on the maintenance dosage of 12.5 mg. daily, as it was clearly necessary for their continued health. Their condition improved rapidly, and within about a week they were as well as they had been when under cortisone therapy previously. All the patients have continued in remarkably good health for the past year on this maintenance dosage, and there is nothing to suggest any loss of effect of the cortisone after two years of treatment. It is important to note that none of the patients have, up to the present, developed hypopituitary coma or any of the symptoms which accompany its incipient stages. This may possibly be related to the improved responsiveness to hypoglycaemia.

Effects of Large Dosage

As was recorded in our previous paper, though large dosage of cortisone produced a striking improvement in the physical condition, psychological disturbances changed the patient's attitude so much that prolonged treatment with large dosage was impossible. Similar observations have been made in three further cases given large doses during the past two years. Two of these patients were typical severe cases of post-partum hypopituitarism; the third patient, also female, suffered from hypopituitarism of uncertain aetiology. These patients were given cortisone orally in a dosage of 50 to 100 mg. a day for one to three weeks. There was usually an improvement in the physical condition for two or three days, but then various psychological disturbances occurred. One of these patients had previously been mentally normal, though dulled by the pituitary deficiency. When she was given large doses of cortisone she developed insomnia and had mild delusions. The second patient had always had a psychotic personality. During the control period she suffered from a variety of delusions, though she had lucid intervals lasting a few days. While on treatment she became definitely worse mentally and was very negativistic. The third case is of particular interest.

A woman aged 58 had had typical severe post-partum hypopituitarism since the age of 33. She had been receiving 100 mg. of testosterone weekly for two years before the present admission. During the last few months she had gradually developed, in addition to her hypopituitarism, what appeared clinically to be a true myxoedema (not what is sometimes called pituitary myxoedema), with coarse scaly skin, gross oedema of the orbits and lips, a croaking voice, and a rapidly progressive loss of head hair. Psychologically she varied between torpor and vulgar abusiveness; her behaviour became what is commonly described as "nasty drunk." She was given 100 mg. of cortisone daily for two weeks. This had no recognizable effect on the physical signs of myxoedema, and her mental condition deteriorated further. She was then given 3 gr. (0.2 mg.) of thyroid siccum daily. Within a week the appearances of myxoedema were much diminished and her mental state was improving. At the end of three weeks she had returned to her condition of six months before; she appeared clinically to be an ordinary case of hypopituitarism and was a peaceful and placid woman again. Continued treatment with this dosage of thyroid and testosterone kept her in reasonable health for several months. After this, cortisone (12.5 mg. daily) was then added to the other treatment. This rapidly produced the characteristic improvement in the general condition. After about three or four days she developed a transient diuresis, and within the next two weeks she became able to do all her housework and go out shopping.

Conclusions

Several aspects of the syndrome of hypopituitarism could reasonably be considered as manifestations of the secondary thyroid hypofunction. These include the mental slowness and lack of interest, the physical sloth, the extreme sensitivity to cold, and the absence of sweating; symptoms which are characteristic of myxoedema. It is therefore very interesting that these particular aspects are influenced by cortisone, which is an adrenal hormone, but not by thyroid.

Until ten years ago a variety of treatments were used in hypopituitarism, but, apart from the effect of pregnancy, the results were not impressive. When testosterone was first introduced its value was obvious, and the patients and their relatives usually insisted that the treatment should be continued. Cortisone in small dosage produces even greater enthusiasm, and all the patients treated so far have invariably returned for a further supply of tablets well before their last supply is exhausted.

Testosterone produces in patients with hypopituitarism a sensation of well-being and improves the physical strength and mental activity. It causes a regrowth of pubic and axillary hair and some return of libido. Cortisone has similar but greater effects on the physical and mental activity, though it does not usually restore body hair. We have therefore tried the effect of giving both substances together, but have not observed any definite additive effect apart from that on the body hair. If after a course of this combined therapy the testosterone is stopped and the cortisone is continued alone, the patient's general condition remains as good as before. On the other hand, a patient who has had cortisone and testosterone together is not nearly so well if an attempt is made to continue treatment with testosterone but without cortisone.

It is a common practice to prescribe a combination of many kinds of treatment for hypopituitarism: thyroid, oestrogens, deoxycortone, sodium chloride, and various vitamins. There are theoretical reasons for administering all of these substances, but detailed studies are required to ascertain what effect is actually produced when each of them is administered singly for a period to patients who are being kept on maintenance treatment with cortisone. The only definite observation we have made is that in certain cases the puffiness of the eyes is reduced by a combination of thyroid and cortisone, but not by either given separately.

From our limited experience up to date it seems that cortisone therapy is the most useful method of long-term treatment of patients with hypopituitarism. A dosage of 12.5 mg. orally each day appears to be adequate for maintenance. A dosage of 25 mg. is equally satisfactory, but it does not produce a proportionate improvement in the signs or symptoms. Larger dosage, such as 50 to 100 mg. a day, is very apt to produce transient mental disturbances; this is in marked contrast to the tolerance of large dosage which is shown by patients with rheumatoid arthritis.

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ANALYSIS OF 1,400 CASES OF ACUTE INJURY TO THE HEAD*

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Between the years 1941 and 1951 2,000 cases of acute injury to the head were admitted to the General Hospital, Newcastle-upon-Tyne, and were treated in the department of neurological surgery. Of these, 1,544 were aged 13 and over (1,281 male, 263 female), and 456 were children up to the age of 12. The death rate in this consecutive series of cases was 10.5%.

In this paper a detailed analysis is given of 1,000 of the adults and 400 of the children; these cases were those of the above series who were admitted to hospital between the years 1945 and 1951. The adults were nursed in the department of neurological surgery; most of the children were nursed in the department of paediatrics.

The primary objects of this study were: (1) to determine the sources and causes of acute head injuries that occur in a provincial city and area engaged in the heavy industries of shipbuilding and mining; (2) to set on record a statistical statement of the severity and the nature of the injuries sustained; (3) to analyse the cause of death and to appraise methods of surgical treatment; (4) to inquire into the long-term results with the object of discovering whether and how morbidity can be minimized; and (5) to bring to the notice of the surgical world once again the magnitude and importance of this branch of medicine.

An analysis of 1,000 adult cases is given (Table I). It will be seen that 444 of them, or nearly half the total, were due to road accidents, and just over 19% of these accidents were fatal. Table II shows the great preponderance of these injuries in the productive period of life, underlining once more the serious social and economic aspect of injuries which for the most part should not happen.

Table III shows, what would be expected, a graver prognosis for patients admitted in a state of semicoma and coma.

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TABLE I.—*Analysis of 1,000 Consecutive Adult Cases*

Cause of Injury	No.	Deaths
Road:		
Car	59	12
Motor-cycle	125	25
Pedal cycle	109	17
Pedestrian	151	33
Industry	248	38
Mines	59	7
Home	77	17
Simple fall outside	59	7
Struck by another	28	2
Sport	29	—
Gunshot wound	4	3
Air crash	2	—
Miscellaneous	10	4
Unknown	40	10
Total	1,000	175

TABLE II

Age	No.		Deaths	
	Male	Female	Male	Female
13 to 20	141	43	16	—
21 „ 30	203	23	25	3
31 „ 40	159	15	21	2
41 „ 50	122	29	25	2
51 „ 60	82	33	23	6
61 „ 70	67	23	27	7
71 „ 80	27	22	13	2
81 „ 90	4	7	—	3
Total	805	195	150	25

TABLE III

Level of Consciousness on Admission	No.	Deaths
Consciousness to confusion	724	27
Semicoma	101	27
Coma	175	121
Total	1,000	175

In 940 of the cases the injury was closed, with possible internal compounding; among these there were 151 deaths. Sixty patients had an open injury of the vault, and 24 of them died. There were 221 associated injuries in the 1,000 cases, as follows: abdominal 3 (2 deaths); thoracic 19 (6 deaths); limbs 114 (16 deaths); spine 11 (no deaths); facio-maxillary 74 (9 deaths). Major operations had to be performed in 209 cases (74 deaths) and minor operations in 166 (16 deaths). The duration of stay in hospital averaged 12.9 days. The disposal of those who survived is shown in Table IV.

TABLE IV.—*Disposal of 825 Patients*

Home	756
Rehabilitation centre	18
Convalescent „	12
Military or naval depot	12
Transfer to other centres (thoracic, facio-maxillary, psychiatric)	6
Miscellaneous	21

To complete the analysis of the cases we give (Tables V and VI) some figures relating to the 400 cases of injury to the head in children (up to the age of 12). Of these, 147 were due to road accidents; there were 20 deaths (13.36%). As many as 149 of the 400 children sustained injury as a result of falling from a height; 5 (3.3%) of these died.

Table VII gives details of the level of consciousness on admission. In the great majority of the cases (368) the injury was closed, with possible internal compounding; 26 (7.1%) of these children died. In 32 cases there was an open injury of the vault, with 8 (25%) deaths. Among the 400 cases there were 38 associated injuries, as follows: thoracic, 3 (no deaths); limbs, 20 (2 deaths); facio-maxillary, 14 (no deaths); pelvis, 1 (1 death). A major operation was necessary in 70 cases (6 deaths)

TABLE V.—*Analysis of 400 Consecutive Cases in Children (to Age 12)*

Cause of Injury	No.	Deaths
Road:		
Car	4	—
Pedal cycle	31	3
Pedestrian	112	17
Home	5	—
Fall from height	149	5
Simple fall	41	4
Sport	12	1
Miscellaneous	40	4
Unknown	6	—
Total	400	34

TABLE VI

Age in Years	No.		Deaths	
	Male	Female	Male	Female
Under 1	12	5	—	—
1	12	5	—	—
2	15	15	1	4
3	23	19	1	1
4	31	10	3	—
5	23	14	1	—
6	27	8	6	1
7	28	7	1	—
8	25	11	2	—
9	22	11	3	2
10	28	5	4	—
11	20	3	3	—
12	19	2	1	—
Total	285	115	26	8

TABLE VII

Level of Consciousness on Admission	No.	Deaths
Consciousness to confusion	322	5
Semicoma	27	9
Coma	51	20
Total	400	34

and a minor operation in 27 cases (no deaths)—that is, out of the total 400. The average duration of stay in hospital was 9.3 days. Of the 366 survivors, 351 were discharged home, 7 to a convalescent centre, and 8 to other hospitals.

Cause of Death in Adult Cases

The cause of death in the 175 fatal adult cases is briefly reviewed below.

Group 1. Admitted in Coma

Of the 175 patients admitted in a state of coma, 121 died (69.1%). A high death rate from head injuries sufficiently severe to render a man comatose is, of course, to be expected, particularly as it is in this group that severe associated injuries are encountered. In 80 cases examined at necropsy cerebral contusions and lacerations, and surface and intracerebral haemorrhages, were found in all varieties of combination, degree, and extent. In every case the macroscopical injuries of the brain tissue were judged to be severe enough either to account for or to contribute substantially to the cause of death. In many there were extensive macroscopical injuries to non-vital areas only; in these, however, the physics of injury were such that vital centres (brain stem, thalamus, and hypothalamus) must, to some extent, have been damaged. In those cases in which there was no vital evidence of macroscopical or microscopical damage to the vital centres it was impossible to judge whether presumed submicroscopical damage could have accounted for death.

In all cases in which there was no gross demonstrable damage to the vital centres there was always gross damage to the non-vital areas; in other words, no patient died of uncomplicated concussion. This does not mean, of course, that a patient could not, in fact, die from injuries to the vital centres of submicroscopical dimensions: this problem is still far from final solution.

In no instance did we come to the conclusion that life could have been saved either by surgical decompression or by the turning of a bone flap, since massive oedema of the brain never occurred without septic encephalitis, and since, in those cases in which there was a local blood clot, there was a contusional or lacerational damage in other parts of the brain. From the surgical point of view we came to the conclusion that the only procedure that might have been of value was drainage of the cerebrospinal fluid, either by lumbar puncture or through a trephine hole in the vault of the skull.

Group 2. Cases Admitted in Semicoma

Of the 101 patients found on admission to be in a state of semi-coma, 27 died (26.7%).

At post-mortem examination 10 were judged to have died as the result of irreversible physical injuries to the brain tissues similar in severity and nature to those found in the coma group.

In a further 10 cases there were obvious contusional injuries in non-vital areas, but these were judged not to be irreversible. We came to the conclusion that in these cases a substantial contribution to the cause of death was the effect of injuries elsewhere in the body. This subgroup particularly calls attention to the importance of the integration of the treatment of a patient as a whole and of the close observation of the minutiae of nursing. When a patient, for example, is in a state of shock it is obviously wrong to inflict further shock by, say, reducing a fracture or submitting him to any other operative procedure before it is absolutely necessary. Also, any kind of asphyxia due to a faulty airway will aggravate the cerebral state, as will overheating or the incorrect administration of fluids.

In the remaining seven cases in which there were no injuries elsewhere in the body to contribute to the cause of death, the extent and degree of the damage to the brain was such that we felt that better-designed surgical therapy might have saved lives; this applied particularly in those cases in which there was a large unilateral acute subdural haemorrhage. We are now coming to the conclusion that when, for some clinical evaluation, open operation is deemed necessary acute subdural haemorrhages can be treated most adequately by the turning of a large osteoplastic flap with wide opening of the dura mater.

In actual practice the difficulty, of course, is to correlate the clinical picture with the pathological happenings. Our objective here is to show that in borderline cases of life and death pathological phenomena amenable to surgical treatment do, in fact, occur in a small percentage of cases. Therefore, skilled and painstaking clinical examinations may occasionally meet with gratifying reward.

Group 3. Cases Admitted in a State of Confusion or Full Consciousness

Of the 724 patients who were either conscious or in a state of confusion, 27 died (3.7%). The causes of death can be classified as follows:

(1) Injuries to the brain unassociated with extradural haemorrhage.—There were 19 cases of this type: five patients died from pyogenic infection resulting from massive compound frontal injuries; three died following operations for severe compound frontal injuries (sepsis did not develop); four died from massive intracerebral haemorrhages such as occur from natural processes—although classified as having died from the head injuries, they probably died from apoplexy; six died from lacerations of the brain associated with either subdural or subarachnoid haemorrhages (three of these were over the age of 70); and one died of cerebral thrombosis.

(2) Mild concussional injuries with severe injuries elsewhere in the body.—In these three cases severe associated injuries were the obvious cause of death.

(3) Extradural haemorrhages complicated by injury elsewhere in the brain.—In the three cases in this group there were (*a*) a unilateral extradural haemorrhage, associated

with a subdural haemorrhage on the same side, and cerebral oedema; (*b*) small bilateral extradural haemorrhages, associated with a laceration of the brain and bilateral subdural haemorrhages; and (*c*) an extradural haemorrhage, associated with a large intracerebral haemorrhage.

(4) Uncomplicated extradural haemorrhages.—The following were the findings in the two cases recorded: (*a*) a large extradural haemorrhage due to laceration of the lateral sinus (the onset of compression in this case was so rapid that operation was not possible); (*b*) a large extradural clot developed after operation for the lifting of a simple depressed fracture—the result, probably, of faulty surgical technique.

From the above description it will be seen that a patient can lapse into unconsciousness from a wide variety of causes after a latent interval following a head injury. Nevertheless, in clinical practice it is dangerous not to diagnose every case of latent unconsciousness as being due to compression of the brain by a surface haemorrhage that can be relieved by surgery. In all cases in which there had been a history of a latent interval, whether the patient was admitted unconscious or conscious, the presence or absence of an extradural clot was always determined either in life or at necropsy.

Extradural haemorrhages occasionally occur associated with severe intrinsic injuries in which there has been no latent interval. More rarely, bleeding from a torn dural sinus may be so rapid that the latent interval is virtually non-existent.

Mechanical Forces Causing Brain Injury

By the nature, degree, and distribution of the lesions found at necropsy in many of the brains, it was judged that the head at the time of accident had been subjected to a series of forces, each acting differently. For example, a patient's brain may be injured when he is flung from his seat, when his head strikes a resistant object, or, again, when it is jerked violently backwards in a rebound. From the distribution of the major lesions it was obvious that the hemispheres, rather than the brain stem and cerebellum, take the brunt of the injury. It was also clear that the hemispheres of the brain not only move in relation to each other but they both frequently move across the brain stem to injure it. Subdural and subarachnoid bleeding is caused not only by the tearing of veins that drain from the surface into dural sinuses but also as the result of laceration and contusion. Severe lacerations are almost certainly caused by the impact of the brain on the cutting edges of bone or of dural partitions. A ruptured vessel on the surface can bleed inwards to cause an intracerebral haemorrhage. No special structure remains immune from injury. Linear as well as rotational forces are nearly always active. Whatever the acting force, it is distortion that ultimately produces the pathological lesion. From the post-mortem findings it is impossible precisely to reconstruct the physics of the injury.

Analysis of Operations

The details of the 209 major operations and 166 minor operations carried out in the 1,000 cases are as follows:

Major Operations

Compound fractures of the vault	44
Compound fractures of the base (internal compounding)	3
Closed depressed fractures of the vault	41
Extradural haemorrhages:	
With latent interval	27
Without ,, ,,	5
Acute subdural haematomata	69
Decompressions	2
Enucleation of eye	4
Major lacerations of the scalp	14

Minor operations for minor lacerations of the scalp were done in 139 cases, and for burr-holes for inspection or drainage in 29.

In addition many lumbar punctures were carried out for drainage and diagnostic purposes.

Extradural Haemorrhages

Among the 1,000 adult cases investigated there were 28 cases of extradural haemorrhage with compression of the brain in which there was a latent interval. Operations were carried out in 27 and one patient died before operation could be performed. Of the 27 patients who were operated on, 17 survived and 10 died. The main details are given in Table VIII.

TABLE VIII.—*Massive Extradural Haemorrhages with Latent Period*

Sex	Age	Cause	Site	Source
		Recoveries		
M	22	Fall of 12 ft.	Right temporal	M.M.A.
M	45	Struck by metal strap	,, parietal	Diploic
M	27	Bicycle accident	Occipital	Lateral sinus
M	18	Motor-cycle accident	Right parieto-occipital	M.M.A.
F	55	Knocked down by car	Parieto-occipital	Sagittal sinus
M	43	Fall of stone in mine	Left fronto-parietal	M.M.A. (trunk)
M	13	Knocked down by car	Left frontal	M.M.A. (ant. branch)
M	32	Bicycle accident	Right temporal	M.M.A. (trunk)
M	28	Hit by cricket ball	Left ,,	M.M.A.
M	29	Fall of 15 ft.	,, parietal	M.M.A. (post. branch)
M	34	Motor-cycle accident	Right fronto-temporal	M.M.A. (ant. branch)
M	52	Fall of stone in mine	Left fronto-temporal	Diploic
M	23	Bicycle accident	Left temporo-parietal	M.M.A. (ant. branch)
M	33	Fall of 45 ft.	Left fronto-parietal	M.M.A. (ant. branch)
M	40	Struck by metal sheet	Right parietal	M.M.A. (trunk)
F	62	Fell from ladder	,, temporo-parietal	M.M.A. (post. branch)
M	50	Knocked down by car	Left fronto-temporal	M.M.A. (trunk)
		Deaths		
M	46	Struck by another	Right temporal	M.M.A. (post. branch)
M	44	Fell downstairs	,, temporo-posterior	M.M.A. (post. branch)
M	29	Fall of stone in quarry	Left parieto-occipital	M.M.A. (ant. branch)
M	31	Bicycle accident	Right parieto-occipital	M.M.A. (trunk)
M	25	Motor-cycle accident	Left temporal	M.M.A. (trunk)
M	55	Struck by metal bar	,, ,,	M.M.A. (ant. branch)
M*	25	Motor-cycle accident	Right ,,	Lateral sinus
F	31	Fall of 7 ft.	Left ,,	M.M.V.
M	23	Bicycle accident	Right fronto-parietal	M.M.A.
M	26	Motor-cycle accident	Right temporal	Diploic
F	25	Dragged by rope	Left ,,	M.M.A. (post. branch)

M.M.A.=Middle meningeal artery. * Operation was not performed in this case.

Of the 10 patients who died following operation, it was found at necropsy that in five cases there were other injuries in the brain, such as lacerations, and subdural and intracerebral haemorrhages.

In the four cases in which complications were not found in the brain, each patient had been in a state of deep unconsciousness on admission, and death in every instance was due to brain-stem compression resulting from too-long-delayed operation. Death in the tenth case was due to a post-operative extradural clot after elevation of a simple depressed fracture—the result, probably, of faulty surgical technique.

Based on our experience, our guides for operative procedure are as follows: (1) Whenever possible the operation is carried out under local analgesia, care being taken to procure a free airway and full oxygenization. (2) The clot is widely uncovered, if necessary by a bone flap; we now rarely use the classical subtemporal exposure by the muscle-split method. (3) (*a*) After gentle evacuation of the clot and sealing of the bleeding vessels, care being taken at all stages not to inflict further pressure on the already embarrassed brain, the operation is halted until signs of recovering consciousness are obvious. When this stage is reached the wound can be closed in the usual way. (*b*) If, half an hour after the removal of the blood clot, there is no sign of returning consciousness the dura mater is widely opened. (*c*) If there is still no sign of return of consciousness half an hour after the decompression has been provided, then the temporal lobe of the brain is lifted and the edge of the tentorium severed to relieve possible tentorial herniation.

Crushing Injuries of the Head

For the head to be crushed between two external objects without first being put into violent motion must, by the circumstances of accident, be exceedingly rare. After having applied the strictest criteria we found that only nine cases fulfilled the requirements of a true crushing injury.

If a head be crushed heavily enough it will disintegrate and death will be more or less instantaneous. In our short series, in the eight patients who lived we could recognize three degrees of injury: (1) severe compound fracture with laceration of the brain; (2) compression of the brain and fracture of the skull without compounding; and (3) fracture of the skull without brain compression.

The crushing type of injury is particularly apt to inflict irremediable damage on special structures and the cranial nerves.

The following were sequels of the above eight cases: unilateral deafness in three, labyrinthine injury in one, unilateral blindness in two, unilateral anosmia in one, and squints in three.

One of the examples of crush injury to the head was that of a young miner whose head became trapped between two tubs. He tried unsuccessfully to free himself; the tubs moved towards each other and the man heard a loud cracking sound as his skull fractured. He then felt himself going unconscious and remembered no more until he woke up in hospital 36 hours later to find that an operation had been carried out. On admission he was deeply unconscious. *X*-ray examination of the skull showed that a piece of bone as large as the palm of a hand had been pushed inwards towards the brain. The bone was elevated and the patient made a complete recovery, there being no retrograde amnesia. The particular interest in this case is that forces of compression produced a state of unconsciousness indistinguishable from that caused by change in speed of movement.

Cerebral Injury During Pregnancy

In two instances women were injured when pregnant and in neither case did the injury cause abortion.

One woman aged 20 was two months pregnant when she sustained a compound wound of the frontal bones with laceration of the brain tissue. She also sustained a comminuted fracture of the upper jaw and lacerations about the face. After extensive cerebral, facial, and dental surgical treatment she made a satisfactory recovery. Her child was born at the normal time, was healthy in every way, and remains so at the age of 4 years. Another observation of interest is that the patient's mother has noticed that her daughter has been much more optimistic and even-tempered since the accident, the change no doubt being due to the leucotomizing effect of the injury on the frontal lobes of the brain. Temperamental changes following head injury are almost invariably in the adverse direction.

The second case was that of a woman aged 28 who was eight months pregnant when she was injured. She survived for three and a half days only, but at no time during this period were there any signs of abortion, the foetal pulse being plainly heard until the mother's circulation began to fail on the third day.

Associated Injuries

In cases of head injury associated injuries to the face, body, and limbs are common. Dislocation of the cervical spine with cord contusion is a well-known complication, as are injuries to the pleura and lungs.

We are, however, particularly anxious to call attention to the facio-maxillary problem which occurs in head injuries and to the necessity for co-operation between the neurological and the facio-maxillary surgeon.

Apart from severe lacerations about the face and scalp that necessitated special plastic repair, 17 complicated fractures of the jaw were treated by our colleague Mr. Godfrey Hutchinson, in his dental department.

When a fracture of the jaw is associated with a state of concussion the decision of when to operate is one which requires considerable surgical experience and judgment. As regards concussion it is wiser to delay facio-maxillary treatment until the patient is well on the way to recovery. On the other hand, if repair of a fractured jaw is delayed too long a satisfactory end-result is jeopardized. It has been our experience that when a mouth injury does not immediately interfere with breathing, treatment of a fracture of the jaw can be postponed until the third day, provided systemic antibiotic treatment is started immediately.

Microscopical Examination of the Brain Stem*

Of the brains obtained whole at post-mortem examination and hardened in 10% formalin, the brain stems of 50 have been cut in their longitudinal axis and examined microscopically.

In five cases there was evidence of gross contusions, the microscopical details of which were similar to those found in the hemispheres. In themselves, these contusions were judged to be severe enough to account for death; in other words, the vital centres had been irrevocably damaged. From the sections it was obvious that post-traumatic hemiplegia must, on occasion, be due to brain-stem damage, the crus cerebri in one case having been torn. Brain-stem and basal ganglia damage may occasionally result from the tearing effects of haemorrhages that start at the surface.

Injuries undetectable by naked eye were easily demonstrable in 10 cases by magnification and showed as typical contusions. Indeed, it is becoming increasingly obvious that in many of the cases that end in death the brain stem has been injured in a physical way. Whether these lesser contusions could in themselves have accounted for death it has not yet been possible to judge; they must, however, have substantially contributed to it.

By definition, presumed injuries of submicroscopical dimensions cannot, of course, be seen through the microscope, but this does not mean that they do not in fact exist; newer methods might demonstrate them. Damage to neurones can be direct or indirect through injury to their supplying blood vessels. No uniform pattern of change in angio-architecture can be determined in the brain stem.

Follow-up Reports

An inquiry was made into the long-term results of 250 consecutive adults who were injured during the years 1949 and 1950. The survey was carried out by means of a questionary, and 236 replies were received.

Of these, 169 patients reported that they had returned to normal work and 57 to light work, but 38 of these were eventually able to resume their original work, giving a total of 207 who finally were able to return to normal employment. Nineteen have remained on light work up to the time of writing. Ten have so far not returned to any form of work. Of the 226 patients resuming work of any kind only 10 have been unable to work regularly.

Seventy-eight patients were free from symptoms on leaving hospital; the symptoms of the remaining 158 were headache, dizziness, loss of smell and taste, and tinnitus. Four patients reported attacks of black-outs.

Changes in personality were reported in 49 cases, severe changes such as mental delusions occurring in only three, the remainder being lack of concentration, bad temper, depression, nervousness, and loss of memory.

The average length of time after discharge from hospital before starting work and the type of work undertaken are given in Table IX.

*This is a preliminary statement on work being carried out in the Research Laboratory of the Department of Surgery, University of Durham.

A similar inquiry was made into the long-term results of 100 children who had received injuries to the head during the years 1949 and 1950; this group was also consecutive.

TABLE IX

Type of Work	Average Period After Discharge Before Resuming Work
Return to normal work	10½ weeks
Return to light work and then normal work resumed	27 ,,
Remaining on light work up to date	32 ,,
Worked irregularly	16 ,,

The survey was carried out by means of a questionary to the parents; 82 replies were received.

Of these children, 51 were of school age when injured, 30 were below that age, and one child was already mentally retarded and unable to attend school.

Forty-three children were able to return to school in their pre-accident class and were able to compete with their age groups. In eight cases the educational standard was affected, the children either being returned to their original class but not moved up with their age group in the normal way or, immediately on return to school, being found to be below standard and placed in a lower class. In these eight cases it is judged that an intellectual injury of some degree has occurred which is likely to influence adversely the scholastic career of these children for the rest of their lives.

Fifty-two children were free from symptoms. Thirty complained of headache and/or dizziness. Fits were reported in four cases.

Changes in temperament were noticed in 27 instances, the main symptoms being nervousness, lack of concentration, faulty memory, bad temper, and bed-wetting, the parents stating in each instance that these manifestations had not been present before the injury.

Discussion

From the figures announced by the Ministry of Transport 5,250 people died during 1951 as the result of injuries received on the roads. So far as can be estimated, at least 60% succumbed as a direct result of injury to the head, and for every death four or five people receive non-fatal injuries.

This subject is important, not only because of the magnitude of these figures but because healthy people, not those already incapacitated by disease, lose their lives or are maimed. Indeed, the economic loss to the nation because of injuries to the head is enormous. Our figures, however, show that road carnage constitutes only 44% of the total number maimed or killed, the remainder being due to accidents in industry, in the mines, in the home, etc.

To meet the increasing needs of cerebral trauma, not only are further facilities for treatment and rehabilitation necessary but postgraduate schools at university level must soon be established for the instruction of those whose responsibility it will be to care for the head injured away from special centres. Whether such centres should be named "head injury" or "traumatic" is of little importance. A seven-day, 24-hour service is necessary, including facilities for radiology and for all other ancillary investigations. Here again we should like to call attention to the necessity for the closest co-operation between the neurological and the facio-maxillary surgeons in the treatment of head injuries.

The imperfect liaison between the hospital and the general practitioner has been, and still remains, a weak link in the problem of head injury. We believe that much advantage would accrue from visits by the general practitioners to patients in hospital during the acute stages of the injury, and this important postgraduate association should be fostered. Also, much waste of man-power could be avoided if, when the time comes for consideration of a patient's return to work, a conference between the general practitioner and the specialist were held in the patient's home surroundings when every aspect of the case could be reviewed. In this way unnecessary hardships could be eliminated and extremes of judgment tempered.

Finally, our post-mortem studies have shown that in a considerable percentage of deaths the injuries received are of such magnitude that they must be irreversible from the moment of infliction. Therefore, again we should like to stress the importance of prevention in the solution of this problem, which should be constantly in the minds of the medical profession, the ruling bodies, and the general public. The chance of serious injury about the head to the individual remains far too high.

Summary

Between 1941 and 1951 2,000 cases of acute injury to the head were admitted to the General Hospital, Newcastle-upon-Tyne. The results of an analysis of 1,400 of these (1,000 adults and 400 children) are given. In the 1,000 adult cases there were 175 deaths, 87 of them due to road accidents; 38 of the deaths resulted from accidents in industry. Of the 175 patients admitted in a state of coma, 121 died. There were 28 cases of extradural haemorrhage with compression of the brain in which there was a latent interval of consciousness: one patient died before operation was possible; of the 27 operated on 17 survived and 10 died.

Of the 400 cases in childhood (up to the age of 12 years) 147 were due to road accidents and 149 to falling from a height: 34 of the children died, 20 of them having been admitted in a state of coma.

CLINICAL AND EXPERIMENTAL STUDY OF SEGMENTAL PAIN FROM THE SHOULDER

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The pain from diseases of the shoulder such as supraspinatus tendinitis or capsulitis is always referred. Although radiation to the arm and hand has been recorded, the distribution of this referred pain has received scant attention in studies of this common group of diseases from orthopaedic sources, nor indeed has it often been mentioned. The importance of its recognition lies in the differentiation from other causes of referred pain into the upper limb, so that unnecessary mistakes in diagnosis can be avoided. Further, clinical and experimental studies of this sort may shed light on the problem of referred pain and on the segmental supply to the shoulder-joint and related structures.

The pain is diffuse and deep, and can be reproduced by experimental noxious stimuli in several ways: one is by injections of 6% saline into the deep structures around the joint. If carried out accurately this method correlates the structure of origin and the segmental reference arising therefrom. It also closely simulates the pain found in clinical cases. Kellgren (1949), in

an extensive review of this subject, advises that each investigator should become his own guinea-pig, because by this painful experience much can be learned, not the least being the difficulty of finding suitable expressions to describe it. In a series of such experiments carried out on myself, the deep pain had a "metallic" quality, but as this is clearly an ambiguous description, meaning nothing to anyone except to me, the simple term deep pain is adhered to. As its name implies, the pain is felt deep in and not on the skin, because it is due to noxious stimuli acting on the spinal segments. This causes a false localization of the pain through unknown phenomena occurring in the central nervous system. It has a maximum intensity proximally and fades peripherally. Patients have described it as "running down the bone and out through the fingers."

Kellgren (1938) showed that experimentally produced pain from interspinous ligaments was always a diffuse segmental pain if the stimulus was strong enough. This also holds for the short tendons and muscles of the shoulder, even though these structures are not centrally placed, as are the interspinous ligaments. I found that irritation of the supraspinatus tendon or muscle belly produced deep pain on the outer aspect of the arm, and sometimes in the forearm and thumb. After the initial injection, which always produced the diffuse segmental pain immediately, the pain could be reproduced hours later by moving the shoulder. On injection of the supraspinatus muscle belly a spot was found that produced a continuous band of reference along the length of the limb (Fig. 1). Local tenderness was also noticed. The segmental pattern of this false localization is discussed later.

FIG. 1.—The spinal segmental distribution in several injections of 6% saline into the supraspinatus muscle and tendon. Oblique hatching indicates muscle; transverse hatching and stippling indicate tendon. The arrows show points of injection.

Present Investigation

The clinical cases and the segmental pain they displayed are here described. During this study a special clinic was opened, so that the questioning and examination of the patients and the charting of the referred pain could be carried out leisurely, which, as every orthopaedic surgeon knows, cannot be done during the hubbub of a routine orthopaedic clinic. In 8 out of 26 patients with supraspinatus tendinitis the pain was referred to the outer aspect of the arm and lower part of the deltoid muscle in an area that reached to just above the elbow (Fig. 2). It was occasionally referred as two narrow bands, on the antero- and postero-lateral aspects of the arm (Fig. 3). In 18 cases the pain radiated down the entire length of the antero-lateral aspect of the upper limb, terminating at the base of the thumb (Fig. 4). The thumb, forefinger, or middle finger was included either singly or together in many cases, with a distinct predominance in the radial fingers.

In 15 patients with spasm of the short rotator muscles associated with tendinitis or injury, and in whom the shoulder was partially stiff, the pain was widely referred to the area of the deltoid muscle and outer aspect of the arm to terminate above the elbow (Fig. 5).

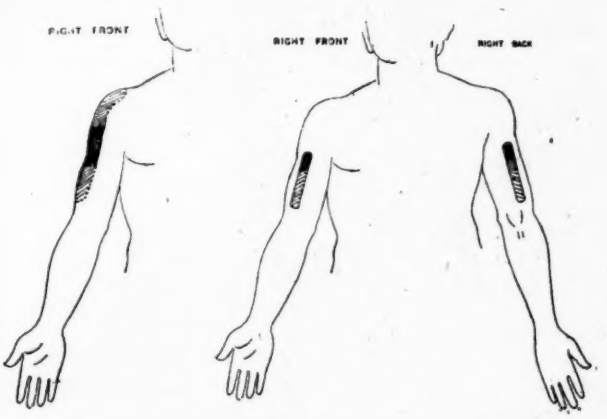

FIG. 2 FIG. 3*a* FIG. 3*b*

FIG. 2.—The average distribution of pain in eight cases of supraspinatus tendinitis. The dark area indicates maximum intensity. This corresponds to the fifth cervical segment. FIGS. 3*a* and 3*b*.—A variation in the reference of the pain in supraspinatus tendinitis, as antero- and postero-lateral bands.

In 35 cases of "frozen" shoulder the pain radiated from the epaulette region into the arm, in many spiralling across the dorsal aspect of the forearm to reach the dorsum of the hand (Fig. 6). Occasionally the pain was referred along the antero-lateral aspect of the forearm to reach the palm (Fig. 7). One or all of the fingers were often included, and there was a distinct tendency for predominance in the middle, ring, and little fingers. In a few the pain was referred to the side of the neck and cheek or to the inner side of the arm and chest wall (Fig. 8). In six cases the pain was referred diffusely to the whole arm, but with accentuation in certain segments (Fig. 9). As was to be expected, a quantitative increase of the diffusion of the deep pain occurred in the more extensive lesions, and this will be discussed elsewhere.

FIG. 4.—The distribution of pain in 18 cases of supraspinatus tendinitis. The fifth and sixth cervical segments are probably involved. The numerals indicate a preponderance of pain in the digits on the radial side of the hand.

Discussion

In other words, despite the diffuseness and difficulty of description and location of this pain, a distinct segmental pattern was displayed.

Head (1893, 1900) and Foerster (1933) depicted the fifth and sixth cervical dermatomes as occupying the antero-lateral aspects of the upper limb, extending to the base of the thumb. If it is assumed that the supraspinatus muscle and tendon are supplied by the fifth and sixth cervical segments through the supraclavicular nerve, then in disease of these and related structures it is probable that the referred pain will appear to be blended and shared in varying degree between them. This is because of the close association of the two spinal segments in the formation of their nerve supply. In any case, the pain may not involve the whole segment of reference (Hilton, 1950). This is borne out by experimentally produced deep pain in the instance of this tendon. Anatomical variations, such as pre- and post-fixation of the brachial plexus and the segmental preponder-

ance in the formation of peripheral nerves, must have a considerable influence on the distribution and fluctuation of referred pain in the upper limb, and probably accounts for the surprisingly high or low segmental reference in some cases of shoulder disease. Kellgren (1939) has shown the significance of anatomical variations in the instance of the lumbar spinal roots. The segmental impression of deep pain from the supraspinatus tendon and related structures corresponds to the dermatome chart of Last (1949) and closely approximates to the segmental distributions of Kellgren (1938) in many injection experiments.

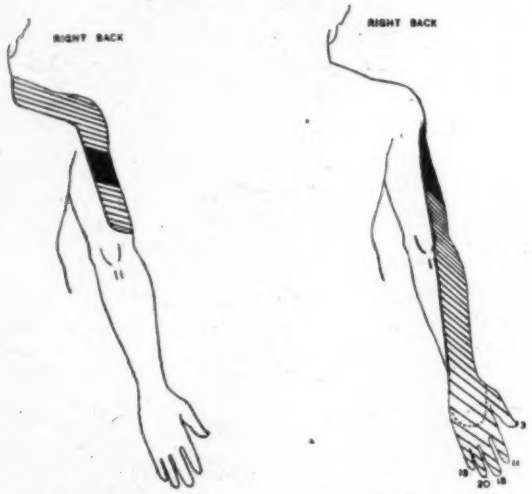

FIG. 5 FIG. 6

FIG. 5.—The average distribution of referred pain in 15 cases of spasm of the rotator cuff muscles. There is a broad band of reference in the fifth cervical segment, and perhaps even wider. FIG. 6.—The average distribution of referred pain in 35 cases of "frozen" shoulder. The numerals indicate a preponderance of pain in the digits on the ulnar side of the hand. The fifth to the eighth cervical segments are represented.

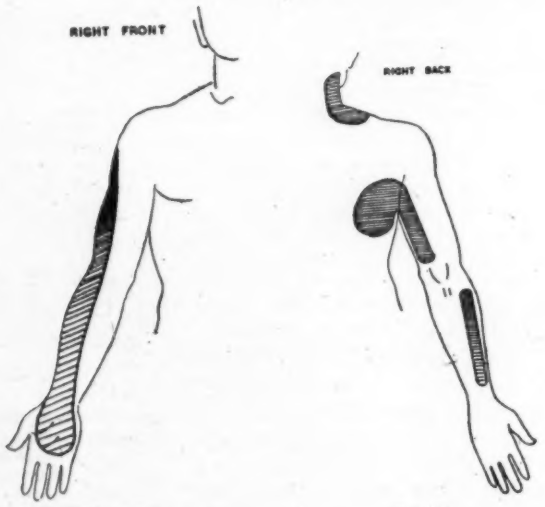

FIG. 7 FIG. 8

FIG. 7.—The distribution of pain in "frozen" shoulder when it radiates to the palm. FIG. 8.—This diagram indicates the wide areas of reference possible in lesions of the shoulder (see text).

The fifth and sixth cervical segments are usually said to supply the shoulder-joint itself (*Gray's Anatomy*, 1949). In "frozen" shoulder, however, as has been shown, the segmental reference may extend from the fifth to the eighth cervical segments, and sometimes more. The occasional higher or lower reference may be tentatively explained by the anatomical variations mentioned above, or there may be a central spread in the spinal cord, on the basis of the wide intersegmental synapses in the tract of Lissauer, as postulated by Earle (1952). This distribution closely follows the dermatome chart of Last (1949) and the spinal segmental patterns of Kellgren (1938) formed by experimentally produced pain from the interspinous ligaments. It does not conform to the "strip" pattern, so popular nowadays, to be found in papers by Keegan and Garrett (1948), Young, (1949) and Walshe (1952), nor indeed to the map in Lewis's (1942) book, in which the dermatome of the eighth cervical segment occupies territory on the inner side of the arm. It is to be clearly understood that the pain is not actually in the anatomical entity known as a "dermatome," which is an area of skin, but, all the same, diffuse and deep as it is, the central misinterpretation of its distribution is that given above.

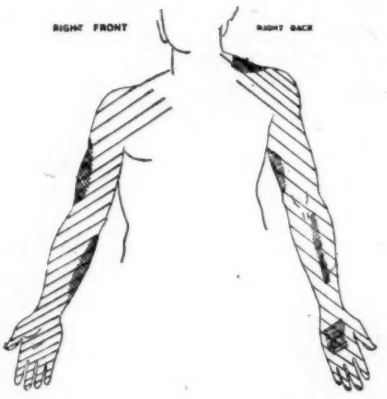

FIG. 9*a* FIG. 9*b*

FIGS. 9*a* and 9*b*.—The distribution of pain in the whole arm in six cases of frozen shoulder. The dark shading indicates accentuation in certain segments.

These latter conceptions ignore the axial lines. This applies particularly to the dermatome of the eighth cervical segment, which is usually the lower border of the segmental reference. Since all, or mainly the ulnar, fingers were included in referred pain from "frozen" shoulder it does seem that the eighth cervical segment was usually the lowest to be stimulated (Fig. 6). Thus when the capsule of the shoulder-joint was widely irritated and was the source of the noxious stimuli, the pain was falsely located in the territory between and cephalic to the axial lines. Further, Last (1949) and Hilton (1950) suggest that the segmental and the nerve supply of the muscles are the same as those of the joint they move, so, according to this reasoning and from the evidence deduced above, the segmental supply to the shoulder must span the fifth to the eighth cervical segments at least, without allowing for any anatomical variations. This is supported by the charts depicted in *Gray's Anatomy* (1949), but awaits definite anatomical proof.

The explanation of diffuse pain in the "whole" arm is bound up with the mystery of referred pain, and it is not my intention to become involved in this paper in a discussion of the various hypotheses on this abstruse subject, or to discuss the peripheral or central mechanism that may be involved. Those interested will find recent conceptions in Sinclair, Weddell, and Feindel (1948), and Hardy, Wolff, and Goodell (1952). But it is extremely unlikely, as is so often suggested by writers on physical medicine, that the entire brachial plexus becomes "sensitive" in acute lesions of the shoulder, to account for the widespread reference of the pain. It is much more likely to have a neuro-anatomical basis from phenomena occurring within the central nervous system.

Summary

Pain from lesions of the shoulder is usually a referred deep pain. Experimentally produced referred pain from the shoulder closely simulates that found in disease.

The referred pain from various lesions of the shoulder, although diffuse, displays a distinct segmental distribution.

It is suggested that this furnishes evidence to support the opinion that the fifth to the eighth cervical segments supply the shoulder.

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FURTHER OBSERVATIONS ON THE METABOLIC STIMULATING EFFECT OF SALICYLATE

BY

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It has been shown (Cochran, 1952) that salicylate causes a pronounced and progressive increase in oxygen consumption when given in full therapeutic dosage to normal and subacute rheumatic subjects. It was suggested that this effect of salicylate might be of fundamental importance in the therapeutic action of the drug. The present paper is a continuation of this work and concerns two further aspects. Firstly, is seemed possible that salicylate might behave in an anomalous fashion in the acutely ill febrile patient, and therefore the effect of the drug on oxygen consumption in the treatment of acute rheumatic fever has been studied. Secondly, it is well known that salicylate (*ortho*-hydroxybenzoate) is effective in the cure of acute rheumatic manifestations, while its isomers (*para*- and *meta*-hydroxybenzoate) are inactive. The effect of these isomers on oxygen consumption has been studied.

Method

Oxygen consumption was measured, using a closed-circuit type spirometer, and the values obtained were corrected for temperature and barometric pressure. The rheumatic fever patients had three consecutive five-minute tracings taken each morning at a constant time and the results were averaged. This routine was continued throughout the course of treatment. When it was desired to test the effect of a single dose of a drug each subject acted as his own control and was in the fasting state. After two or three consecutive tracings a single dose of the test drug was given by mouth and serial estimations of oxygen consumption were made at roughly 20-minute intervals for two to three hours.

Results

Observations were made on three patients admitted with acute rheumatic fever who received aspirin in full therapeutic doses of approximately 2 g. four-hourly. In each case the expected clinical improvement with relief of arthritis and fall in temperature occurred within 24 to 48 hours of starting treatment. In Figs. 1 to 3 the daily levels of oxygen consumption are plotted with the oral temperature obtained just prior to the oxygen measurement. In Fig. 1 it is seen that although the temperature has fallen by 4.8° F. (2.7° C.) the level of oxygen consumption has actually increased. When aspirin is gradually withdrawn the metabolic rate slowly falls. In Fig. 2 the temperature has fallen by 4° F. (2.2° C.), but the metabolic rate remains at an elevated level until an abrupt fall occurs when aspirin is suddenly withdrawn. In Fig. 3 there is a similar pattern of changes. The abrupt fall in temperature is accompanied by a progressive rise in oxygen consumption, which again falls only when aspirin treatment is stopped.

A fourth patient was treated at first with sodium salicylate and sodium bicarbonate in equal doses of 20 gr. (1.3 g.) four-hourly. The initial clinical response was satisfactory, but on reducing the dosage a relapse occurred and treatment was changed to aspirin. A second relapse followed aspirin withdrawal, and a further course was given. The relationship of relapse to oxygen consumption is shown in Fig. 4. It is seen that recrudescence of symptoms occurred when the oxygen consumption had fallen to low levels, either in reduction of dosage or withdrawal of salicylate.

A comparison was made of the effects on oxygen consumption of single 3-g. doses of sodium salicylate and aspirin and single 5-g. dosage of the *para*- and *meta*-hydroxy isomers of salicylate. The tests were carried out on the same convalescent patient, and the results are shown in the Table. Sodium salicylate and aspirin caused respectively a 12% and 11% maximal increase in oxygen consumption, while the two isomers were without significant effect. Two convalescent patients were given the isomers over a four-day period in doses of approximately 2 g.

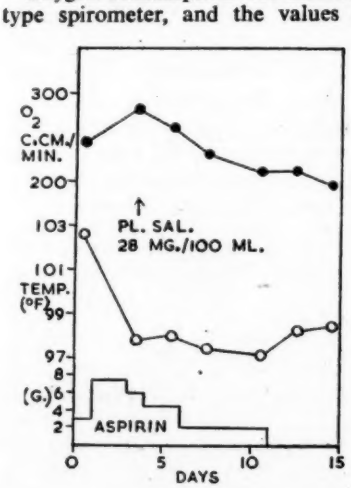

FIG. 1

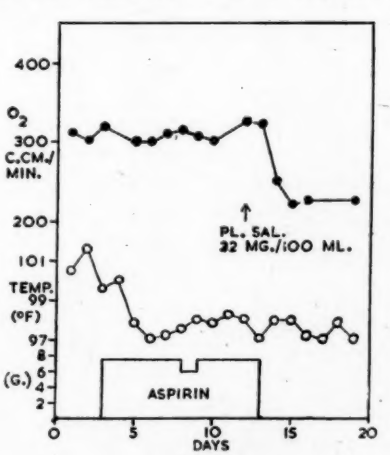

FIG. 2

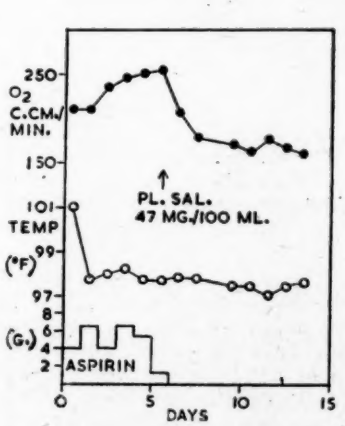

FIG. 3

FIG. 1.—Effect of aspirin on oxygen consumption and body temperature in a patient with acute rheumatic fever. Although the temperature has fallen by 4.8° F. (2.7° C.) the level of oxygen consumption has increased and slowly falls when aspirin is gradually withdrawn. FIG. 2.—Results obtained in a second patient with rheumatic fever. The temperature has fallen by 4° F. (2.2° C.), but the metabolic rate remains at an elevated level until an abrupt fall occurs when aspirin is suddenly withdrawn. FIG. 3.—Results obtained in a third patient with acute rheumatic fever. An abrupt fall in temperature is accompanied by a progressive rise in oxygen consumption, which falls only when aspirin treatment is stopped.

four-hourly. There was no significant increase in oxygen consumption with either *para-* or *meta-*hydroxybenzoate (Figs. 5 and 6).

Discussion

Barbour (1919) and Barbour and Devenis (1919) stated that salicylates increase the metabolism in afebrile subjects but lower it in febrile patients. These workers used a Benedict respiration chamber, and observations were made after the ingestion of single 1-g. doses of aspirin. It would seem that the pharmacology of salicylate, and in particular the effect of the drug on oxygen uptake, would be most profitably studied where full therapeutic doses are being given and are having the desired beneficial effect, as in the present study.

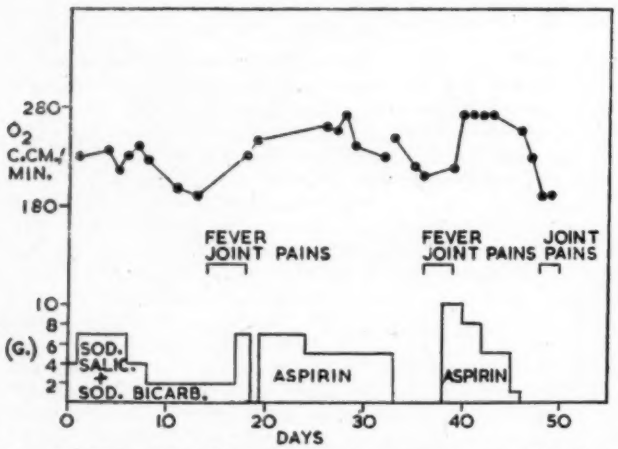

FIG. 4.—The relationship of relapse to oxygen consumption in a patient with acute rheumatic fever treated with salicylate. Recrudescence of symptoms occurs when oxygen consumption has fallen to low levels, either on reduction of dosage or withdrawal of salicylate.

Results Obtained when Single Doses of Sodium Salicylate, its Isomers, and Aspirin are Given on Different Days to a Convalescent Rheumatic Patient. Sodium Salicylate and Aspirin (3 g. Dose of Each) Cause Respectively a 12 and 11% Increase in Oxygen Consumption while the Isomers Para- and Meta-hydroxybenzoate (one 5-g. Dose of Each) are Without Significant Effect

Oxygen Consumption c.cm./min., at N.T.P.

Average 3 Control Values	229	209	219	199
Drug Oral	Sod. Salicylate 3 g.	Aspirin 3 g.	Sod. *p*-OH-benzoate 5 g.	Sod. *m*-OH-benzoate 5 g.
20 min.	230	219	204	205
40 „	223	203	206	191
60 „	234	209	206	191
80 „	256	228	206	182
100 „	247	232	210	189
120 „	252	226	215	200
140 „	239	217	205	191
160 „	—	223	210	185
Maximal increase	12%	11%	Nil	3% (20 min. only)

The metabolic rate rises in fever, and it has been estimated that it increases 7% for every degree F. of fever. In the patients studied the acute stage of rheumatic fever was associated with a raised metabolic rate. It is assumed that in an untreated case undergoing natural remission the fall in temperature and subsidence of symptoms would be accompanied by a parallel reduction in the level of oxygen consumption. In the treated rheumatic patients it has been shown that the level of oxygen uptake either increases or remains at an elevated level, while the temperature falls and symptoms are relieved. It is only on stopping salicylate therapy or on reducing dosage that the oxygen uptake falls to normal or near normal levels. There would seem to be no doubt that salicylate has a metabolic stimulating effect in the febrile acute rheumatic patient; the increase in metabolism due to the drug is equal to or greater than the decrease in metabolism due to the lowering of temperature, and the net result is the maintenance of a high metabolic rate while full therapeutic doses are being given.

It is important to determine if the metabolic stimulating effect of salicylate is an essential part of the therapeutic action of the drug. It has been shown that the effect is not shared by the closely related salicylate isomers, *para-* and *meta-*hydroxybenzoate. There is no significant increase in oxygen consumption when these substances are given over a four-day period in amounts equivalent to full therapeutic dosage of salicylate. The salicylate isomers are known to be quite ineffective in the relief of acute rheumatic manifestations.

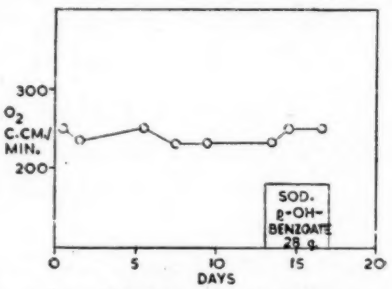

FIG. 5.—Administration of sodium *para-*hydroxybenzoate in doses of 2 g. four-hourly for four days has no significant effect on oxygen consumption.

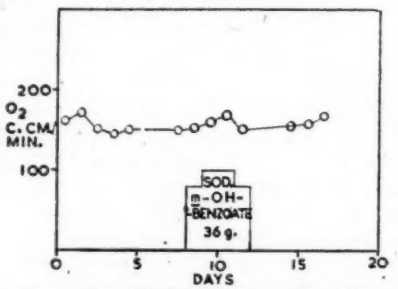

FIG. 6.—Administration of sodium *meta-*hydroxybenzoate in doses of 2 g. four-hourly for four days has no significant effect on oxygen consumption.

Further work is in progress to attempt to elucidate the therapeutic importance and the nature of the metabolic stimulating property of salicylate.

Summary

It has previously been shown that full doses of salicylate greatly stimulate the metabolic rate of normal and subacute rheumatic subjects. The present study concerns the metabolic effect of full therapeutic doses of salicylate in the treatment of acute rheumatic fever. Fall in temperature and relief of symptoms are associated with the maintenance of the original high level of oxygen consumption, and the level falls only when the drug is withdrawn or dosage reduced. It is concluded that salicylate has a metabolic stimulating effect in the acutely ill rheumatic patient.

The isomers of salicylate, *para-* and *meta-*hydroxybenzoate, which are without effect in the relief of the acute rheumatic state, do not significantly alter the metabolic rate of convalescent patients.

I am greatly indebted to Professor Sir John McNee and Dr. James Reid for their constant help and criticism.

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Study Abroad, vol. 6 of which has just been published by Unesco (H.M. Stationery Office, 7s. 6d.), gives information on over 45,000 fellowships, scholarships, and other subsidized opportunities for educational travel. These facilities provide for study in almost every field of learning and in about 60 countries. This new volume appears in a single trilingual edition which replaces the English, French, and Spanish editions of previous years.

"FAILED FORCEPS": A REVIEW OF 100 CASES

BY

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Occipito-posterior positions and deep transverse arrest of the head accounted for over 50% of "failed forceps" cases investigated at the Birmingham Maternity Hospital by Freeth (1950), who found that the maternal death rate was 2% and the total foetal loss was 34%. Earlier, Miller (1928) reviewed a larger series with a maternal death rate of 10% and a total foetal loss of 64%. The reduction in the mortality from failed forceps over two decades has therefore been considerable.

To confirm Freeth's findings and to see if a similar reduction in mortality has taken place in another large maternity hospital, all cases of failed forceps admitted to St. Mary's Hospital, Manchester, during the period January, 1943, to December, 1951, have been reviewed.

Undilated cervix (39%) was the commonest cause of failure. The maternal death rate was 2% and the total foetal loss was 28%.

Incidence

The number of cases admitted each year fell from 17 in 1943 to 1 in 1951 (Table I). As the total number of emergency admissions varied considerably from year to year, the failed forceps cases have been expressed as a percentage of the total emergency admissions. There is a decrease from 3.2% in 1943 to 1.5% in 1948, followed, after an increase in 1949, by a fall to 0.5% in 1951.

TABLE I.—*Incidence of Failed Forceps Cases*

Year	No. of Cases	% of Total Emergency Admissions
1943	17	3·2
1944	15	2·6
1945	17	2·5
1946	12	2
1947	17	2·8
1948	7	1·5
1949	8	2·4
1950	6	1·9
1951	1	0·5

Aetiology

The causes of failure fall into eight groups, and each group is analysed separately (Table II). In certain cases more than one possible cause for failure was present. When this occurred the case has been classified under the more important cause. Thus in the presence of incomplete cervical dilatation along with an occipito-posterior position, the case has been classified under the former condition. When spontaneous delivery occurred shortly before or after admission the cause of failure could not be verified. Such cases have been allotted to Group 8.

TABLE II.—*Details of 100 Cases*

Group	Aetiology	No. of Cases	No. of Primi-parae	Foetal Loss	Maternal Deaths	Baby Dead on Admission
1	Cervix not fully dilated	39	22	14	—	6
2	Occipito-posterior positions	22	19	5	1	1
3	Deep transverse arrest	11	9	2	—	1
4	Brim disproportion (normal foetus)	7	4	4	—	2
5	Contracted outlet (occipito-anterior)	7	7	1	—	—
6	Hydrocephalus	3	1	3	—	2
7	Brow presentation	2	1	1	—	1
8	Unknown	9	6	1	1	1
	Total	100	69	31	2	14

Group 1—Cervix Not Fully Dilated (39 Cases).—All cases were treated expectantly in the first instance (Table III). If full dilatation of the cervix did not occur, caesarean section or forceps extraction after craniotomy was carried out, depending on whether the foetus was alive or dead. Natural dilatation of the cervix occurred in 33 cases. Of these, six were subsequently delivered by natural forces. In 27 cases forceps were applied. This high proportion is partly accounted for by the 10 cases of occipito-posterior position (including deep transverse arrest), and in the other 17 cases there was perhaps a tendency to apply forceps rather readily in the belief that, once failure with forceps has occurred, it is safer—for the baby—to deliver as soon as possible. The onset of foetal distress in one multipara with a rim of cervix was unsuccessfully treated by internal version and breech extraction.

TABLE III.—*Cervix Not Fully Dilated*

Treatment	No. of Cases	Foetal Loss	Baby Dead on Admission	Maternal Deaths
Sedation—caesarean section	4	2	—	—
" —rotation, mid-forceps	10	3	1	—
" —mid-forceps	8	4	2	—
" —low forceps	6	2	1	—
" —normal delivery	6	1	1	—
" —craniotomy, forceps extraction	1	1	1	—
Internal version—breech extraction	1	1	—	—
Sedation—high forceps	3	—	—	—
Total	39	14	6	—

Group 2—Occipito-posterior Positions (22 Cases).—In one case associated with a funnel-shaped pelvis caesarean section was resorted to when attempts at manual rotation failed. In cases in which the foetal heart was still audible at the time of admission there were two stillbirths and two neonatal deaths from intracranial haemorrhage. The maternal death, which was attributed to shock, occurred after manual rotation and mid-forceps extraction.

TABLE IV.—*Occipito-posterior Positions*

Treatment	No. of Cases	Foetal Loss	Baby Dead on Admission	Maternal Deaths
Rotation and mid-forceps	18	4	—	1
Mid-forceps, face to pubes	1	—	—	—
L.S.C.S.	1	—	—	—
Normal delivery	1	—	—	—
Craniotomy and extraction	1	1	1	—
Total	22	5	1	1

Average weight of baby, 7 lb. 13 oz. (3·5 kg.).

Group 3—Deep Transverse Arrest (11 Cases).—All the cases in this group were treated by manual rotation and mid-forceps extraction. Shoulder dystocia caused the only stillbirth among babies alive on admission.

Group 4—Brim Disproportion (7 Cases).—The size of the baby—average weight 9 lb. 4 oz. ± 11.3 oz. (4.2 kg. ± 85 g.)—rather than contracted pelvis was the major factor in causing disproportion. In one case with a normal pelvis the baby, which was dead on admission, weighed 13 lb. (5.9 kg.). The treatment of choice for brim disproportion with a living baby is caesarean section. The poor results with the alternative, high forceps, are shown in Table V.

Group 5—Outlet Contraction (7 Cases).—In seven cases, all primiparae, contracted outlet was stated as the reason

for failure. In only one case, in which the single foetal loss occurred, was pelvic outlet contraction definitely established by the recorded measurements. In this case the intertuberous diameter was 3½ in. (8.3 cm.) and the posterior sagittal diameter 2 in. (5 cm.). With great difficulty an 8 lb. 4 oz. (3.7 kg.) stillborn foetus was delivered with forceps. In the other cases moderate traction with forceps effected delivery. In all the occiput was anterior and in none had episiotomy been performed before admission. I believe that soft-tissue resistance, rather than bony disproportion, caused the failure or was an important contributing factor.

TABLE V.—*Brim Disproportion*

Treatment	No. of Cases	Foetal Loss	Baby Dead on Admission	Maternal Deaths
L.S.C.S.	3	—	—	—
High forceps	2	2	—	—
" " perforation cleidotomy	1	1	1	—
Craniotomy	1	1	1	—
Total	7	4	2	—

Average weight of baby, 9 lb. 4 oz. (4·2 kg.).

Group 6—Hydrocephalus (3 Cases).—The diagnosis was made by the size of the head and the great width of the cranial sutures on vaginal examination. Treatment was by craniotomy. Bilateral episiotomies had been made in one case in which the greater part of the head lay above the brim, but such moulding had occurred that it was also visible at the vulva.

Group 7—Brow Presentation (2 Cases).—One of these cases was treated by caesarean section and the other by craniotomy, as the baby was already dead. In the latter case even after craniotomy great difficulty was encountered in delivering the head. Exploration of the uterus revealed an extensive rupture of the lower segment which was treated by supravaginal hysterectomy. The patient's recovery was complicated by a temporary uretero-vaginal fistula, but this closed by the twentieth day and she eventually did well.

Group 8—Aetiology Unknown (9 Cases).—Normal delivery or an easy low forceps extraction successfully terminated the labour in eight cases. The ninth ended fatally (Table VI). After failing to deliver with forceps the family medical attendant performed internal version and unsuccessfully attempted breech extraction. On admission the dead baby was delivered up to the head, and maternal shock was present. The after-coming head was delivered easily by the Mauriceau–Smellie–Veit manœuvre under a general anaesthetic, the third to be administered. The uterus was not explored and the third stage was normal. Twelve hours later the patient's condition deteriorated and death occurred 24 hours later. Necropsy revealed a ruptured uterus which was unsuspected until the general condition was such that surgical intervention was no longer feasible.

TABLE VI.—*Aetiology Unknown*

No.	Method of Delivery	Primipara	Time Elapsed Since Failure	Foetal Loss	Maternal Deaths
1	Born before arrival ..	—	2½ hours	—	—
2	Normal delivery on admission ..	—	1 "	—	—
3	" " "	1	3½ "	—	—
4	" " "	1	1 "	—	—
5	" " "	1	1½ "	—	—
6	Easy low forceps on admission ..	1	3 "	—	—
7	" " "	1	2 "	—	—
8	" " "	1	1½ "	—	—
9	Delivery of after-coming head	—	1 "	+	+

Munro Kerr and Chassar Moir (1949) say, "Version (after failed forceps) is never worth while; not one in two children is saved, and more than 10% of mothers are lost from rupture of the uterus, shock, or sepsis."

Prophylaxis

Many cases could be prevented if the accoucheur constantly kept in mind the criteria for a successful forceps delivery—namely, (1) no cervix palpable; (2) the head deeply engaged; and, if the forceps is to be applied in the home, the head should be visible on separating the labia; (3) the occiput anterior; (4) no marked contraction at the pelvic outlet; and (5) the bladder and rectum empty.

Even with a visible head the abdomen should always be examined to exclude the hydrocephalic which has so moulded that the greater part is above the brim yet is visible at the vulva. If the cervix is palpable (so often said to have re-formed) after the induction of anaesthesia, the interests of mother and baby are best served by graceful retreat without applying forceps. (An exception, however, may be made in respect of a multipara with a rim of cervix which responds easily to manual dilatation.)

Principles of Treatment

Once failure occurs the treatment of shock, if present, should be the first consideration. In this event it is advantageous in domiciliary practice to call an obstetrical flying squad, which should then assume responsibility not only for resuscitation but also for the subsequent delivery.

Failure to deliver with forceps, using moderate traction, should not be regarded with shame. On the other hand, persistent attempts to deliver by brute force constitute bad practice.

Whenever possible the doctor should accompany his case to hospital, giving full particulars of the labour, with special reference to the time of full dilatation, number and type of anaesthetics administered, and the previous obstetrical history. If this is neglected, drowsiness of the patient may lead to the failure to elicit vital information.

In hospital the patient is admitted to a "suspect" ward, as every case must be regarded as potentially infected. (In the present series the incidence of notifiable pyrexia was 18%.) The interests of the individual in such a case demand antibiotics. Unfortunately, however, the routine administration of these drugs may lead to the subsequent production of resistant strains.

It will often be advisable to set up a 5% glucose intravenous drip as soon as possible, in view of the fact that many cases are suffering from acidosis and dehydration. It should also be borne in mind that all of these patients have had some form of anaesthesia, and many have had more than one anaesthetic. It is therefore important to ensure that any further anaesthetic is given by a skilled person, that chloroform is avoided, and that it is the last anaesthetic required. With the latter end in view it is considered advisable after delivery to explore the uterus to discover if any damage has occurred.

Discussion

The fall in the annual number of cases is ascribed to three factors: (1) Improved antenatal care, which has reduced the number of home confinements of such abnormalities as brim disproportion, hydrocephalus, and outlet contraction. (2) The stress laid in the modern teaching of obstetrics on the criteria for successful forceps delivery. (3) The appointment of new consultants in the outlying districts since the advent of the National Health Service in 1948. The number of patients confined in hospital was not a factor in the fall, as there were fewer hospital confinements in the Manchester area in 1951 than in 1945.

Contrary to Freeth's findings, the commonest cause of failure in this series was application of the forceps before the cervix was fully dilated, and in at least 50% of the cases the forceps was applied too soon. Unlike Freeth (1950) earlier reviewers (Feeney, 1947; Stacey, 1931) came

to a similar conclusion. Ovarian tumour, constriction ring, or breech or face presentation were not observed, although Freeth found one of each abnormality.

A maternal mortality of 2% and a foetal loss of 28% are similar to Freeth's figures. In the last 25 cases reviewed the total foetal loss was only 8% and all the mothers survived.

Reference to Table VII demonstrates the progressive improvement in the maternal mortality since 1928. Analysis of the deaths in Miller's series suggests that the reduction

TABLE VII.—*Review of Earlier Series*

Author	Location	Year	No. of Cases	Maternal Loss %	Foetal Loss %	Minimal Foetal Loss %	No. of Ruptured Uteri
Gadd	Manchester,	1952	100	2	28	14	2
Freeth	Birmingham,	1950	100	2	34	10	—
Feeney*	Dublin,	1947	77	16·9	60	56	6
Munro Kerr	Glasgow,	1933	70	7	51	?	?
Stacey	Sheffield,	1931	154	15	52	29	?
Miller	Manchester, Glasgow, Edinburgh	1928	558	10	64	23	8

* Does not include any cases in which normal delivery or low forceps without complications to the mother occurred.

in maternal loss is due to the advent of antibiotics and blood transfusion rather than to greater obstetrical skill. Miller's deaths occurred from sepsis (37), ruptured uteri (8), post-partum haemorrhage and shock (6), pneumonia (3). Excluding the deaths from sepsis and pneumonia, maternal deaths were only 2.5%, a figure similar to the two recent series in which none of the four deaths occurred from sepsis.

A similar reduction occurred in the total foetal loss. The minimal foetal loss is the percentage of babies dead on admission. Excluding Feeney's series there has been a change for the better in the type of case. In Miller's and Stacey's series the babies dead on admission were over twice as many as in the two later series. Subtracting the minimal foetal loss from the total foetal loss gives the "actual" loss of babies in hospital. In Stacey's series this was 23% and in the present series 14%. This difference may be accounted for by the more confident and safer use of caesarean section to-day for inertia, brim disproportion, and difficult occipito-posterior positions. Caesarean section was employed only for brim disproportion in Freeth's series, with the result that his "actual" foetal loss in hospital was 24%—1% higher than Stacey's figures 20 years previously.

Summary

A review has been undertaken of 100 consecutive failed forceps cases admitted to St. Mary's Hospital, Manchester, during 1943–51.

The incidence of such cases fell from 3.2% to 0.5% of the total emergency admissions, and reasons for this decline are suggested.

The commonest cause of failure was the undilated cervix (39%).

The maternal mortality was 2% and the total foetal loss was 28%.

Pyrexia was notifiable in 18% of the cases.

A comparative survey of earlier series is presented, and reasons are suggested to explain the gradual improvement noted in the results.

I wish to thank Dr. E. A. Gerrard, Professor W. I. C. Morris, and Dr. J. W. A. Hunter for help and advice in the preparation of this article.

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CRISES IN CONGENITAL SPHEROCYTIC ANAEMIA (ACHOLURIC JAUNDICE)

BY

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Since the observation by Owren in 1948 that in the crisis of "acholuric jaundice" the bone marrow showed hypoplasia of the erythron there have been confirmatory reports in America (Dameshek and Bloom, 1948) and on the Continent (Cremer, 1950; Gasser, 1950). Other than an annotation in the *British Medical Journal* (1949) there has been extremely little comment in this country. Whitby and Britton (1950) merely note Owren's views without comment. Changes in the bone marrow as a cause of "crisis" have by no means reached general clinical assent.

Details of the marrow changes in four crises in three children are presented here, and the probable aetiology of the anaemic crisis is discussed.

Case 1

The patient was first admitted to hospital at the age of 1 month with extreme pallor and a history of icterus neonatorum lasting 20 days. Her haemoglobin was 5.2 g.% and she was thought to be a case of congenital hypoplastic anaemia. A blood transfusion was given and she was discharged. When readmitted two months later with further anaemia (Hb 5.6 g.%) her reticulocytes varied between 2.5

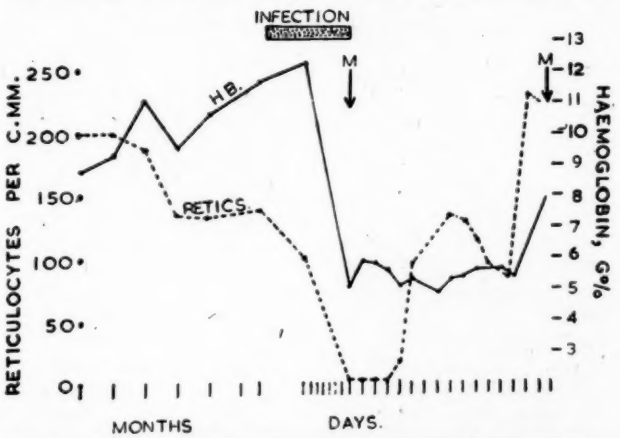

FIG. 1.—Case 1. Showing changes in haemoglobin and reticulocyte level during the first crisis. M = marrow biopsy.

and 4% of 2,250,000 red cells. Spherocytes were seen in the film. She was given a further transfusion and discharged.

She attended the out-patient department for about a year, during which her haemoglobin remained around 8 g.% and her reticulocytes between 3 and 6%.

She then had a crisis. This followed a period of restlessness, fretfulness, cough, and nasal discharge for two weeks, during which time she was seen to become increasingly pale. The course of the crisis may be seen in Fig. 1. No reticulocytes were seen for five days; they then appeared, and increased steadily in numbers over the next nine days, her general condition then returning to the pre-crisis state. Marrow biopsies were taken at the onset of the crisis and after recovery. Marrow pictures were based on counts of

approximately 1,000 cells; the cells were :—*At crisis:* myeloblasts, 1.0; promyelocytes, 4.0; neutrophil myelocytes, 7.75; eosinophil myelocytes, 0.25; neutrophil metamyelocytes, 8.0; eosinophil metamyelocytes, 0.25; neutrophil polymorphs, 18.5; eosinophil polymorphs, 1.25; basophil polymorphs, nil; lymphocytes, 13.0; mononuclears, nil; proerythroblasts, 3.0; eosinophil normoblasts, 2.0; intermediate normoblasts, nil; late normoblasts, nil; unidentified cells, 2.0; haematogones, 37.0; plasma cells, nil; reticulo-endothelial cells, 1.0; mitotic cells, 0.25. *After recovery from crisis:* myeloblasts, 0.25; promyelocytes, 1.25; neutrophil myelocytes, 7.0; eosinophil myelocytes, 1.0; neutrophil metamyelocytes, 9.0; eosinophil metamyelocytes, 0.25; neutrophil polymorphs, 4.5; eosinophil polymorphs, 0.75; basophil polymorphs, 0.25; lymphocytes, 6.0; mononuclears, nil; proerythrocytes, 3.25; early normoblasts, 11.0; intermediate normoblasts, 22.0; late normoblasts, 29.25; haematogones, 2.5; plasma cells, nil; reticulo-endothelial cells, 1.0; mitotic cells, 0.75.

The distribution of primitive cells in the erythron (Fig. 2) shows a general depression in the crisis period.

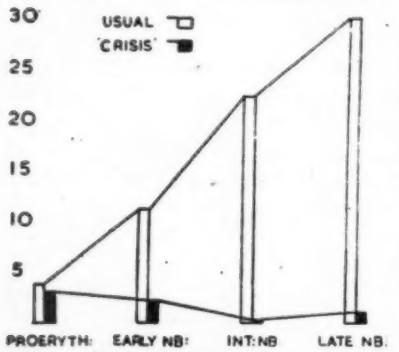

FIG. 2.—Case 1. First crisis. Showing the percentage of cells of the erythroid series seen in the marrow during the crisis period and later in the recovered state ("usual").

She was then followed in the out-patient department for approximately six months, her haemoglobin remaining at about 9 g.% and reticulocytes 4%.

She was then readmitted with a history of anorexia for seven days, abdominal pain and fever for two days, and vomiting for one day. She was afebrile on admission and her bone marrow again showed hypoplasia of the erythron. Her erythrocyte count fell from 3,800,000 to 2,500,000 in five days, the haemoglobin from 8.2 to 5.5 g.%, and the reticulocytes from 133,000 (3.5%) to 35,000 per c.mm. (1.4%). Her reticulocytes remained low for the next four days and then steadily rose during the next week to 350,000 per c.mm. and the blood count steadily returned to its pre-crisis level of between 8 and 9 g. Hb% with 4,000,000 to 4,500,000 erythrocytes. Her marrow again showed hyperplasia of the erythron—that is, the changes seen in the previous crisis were repeated.

Her spleen was then removed. Since that time her haemoglobin has remained in the order of 10 to 12 g.%, and she has shown no anaemic crisis.

Other Investigations.—During her anaemic crisis no changes were seen in her leucocyte count. Erythrocyte saline fragility curves showed haemolysis commencing in 0.67% and complete in 0.4% saline. Coombs's test was negative. The serum bilirubin during the second crisis was 1.3 mg. per 100 ml., a single level done in a quiescent phase being 1.1 mg. per 100 ml. The child's mother has a spherocytic anaemia with abnormal saline fragility, but gives no history of recurrent anaemic crises.

Comment.—This child, who had typical familial spherocytic anaemia, was observed through two crises. Both episodes were preceded by a clinical disorder, the first by an upper respiratory infection, and the second by an intestinal disturbance which may have been an infection. In both crises the usually hyperplastic erythron was replaced by extremely hypoplastic tissue and there was a great fall in peripheral reticulocytes. The first crisis was severe, and was associated with a depression of the bone marrow which lasted at least 10 days. The second crisis was much less severe, and the duration of the hypoplasia seemed to be less. In both instances recovery was spontaneous. No depression was seen in the leucon either in the peripheral blood or in the bone marrow. During the crisis the child was pale and yellowish but not notably jaundiced, and the blood bilirubin did not appear significantly raised from the resting level. Splenectomy effected a clinical cure.

Case 2

This child was admitted in "crisis" at the age of 6½ years. She had been one of twins and had had spastic quadriplegia since birth. No history of anaemic episodes was available.

Examination revealed severe pallor, Hb 3.4 g.%, R.B.C. 1,300,000, and reticulocytes 5,200 per c.mm. The erythrocytes showed marked spherocytosis. Her saline fragility curve was typical of hereditary spherocytic anaemia; haemolysis began in 0.75% and was complete in 0.40% saline. No evidence of serological blood incompatibility was found. Her bone marrow on admission showed considerable depression of erythropoiesis, particularly in the late normoblast stage (Fig. 3).

Immediately after the marrow puncture she was given a blood transfusion; this raised her haemoglobin to the region of 10 g.%, and coincidental with this her reticulocytes rose to 224,000 per c.mm. and remained at about this level for several days.

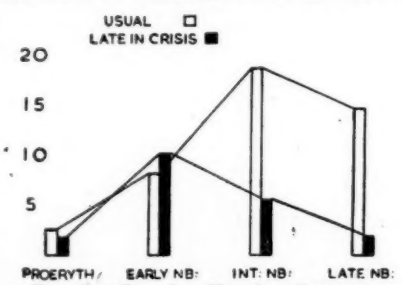

FIG. 3.—Case 2. Showing the percentage of primitive cells of the erythron in the bone marrow during the period of crises and after the recovery from the crises.

Marrow puncture at this time showed hyperplasia of the erythron and a picture similar to that seen in subsequent studies before splenectomy. The leucocyte counts throughout the crises were above what appeared to be a normal level for the child.

She was subsequently discharged for a few weeks and then readmitted for splenectomy, after which her reticulocyte count fell to normal levels, although her fragility curve remained abnormal. She has since then shown no anaemia. Faecal bilirubin excretion during the period of crisis was 19 mg. a day. Later when she came in for splenectomy the level was 62 mg. a day.

Comment.—We were unable to follow the whole course of the crisis in this child. She showed, however, three features: (1) reticulocytopenia and marrow hypoplasia during the crisis; (2) an apparent immediate reticulocyte response to the administration of 2 pints (1,140 ml.) of blood; (3) a relative diminution of faecal bilirubin excretion during the crisis period.

Case 3

This child was first seen when aged 6 years, and was admitted with a history of increasing pallor for about 48 hours. She was extremely pale with a faint yellowish tinge. Her blood bilirubin was 1.8 mg. per 100 ml. Her haemoglobin was 1.3 g.%, R.B.C. 900,000, platelets 47,000 per c.mm., and reticulocytes 14,000 per c.mm. Her erythrocytes showed marked spherocytosis and increased saline fragility. (Haemolysis began in 0.75% and was complete in 0.40% saline.) Her bone marrow showed extreme hypoplasia of the erythron with a few giant proerythroblasts.

A blood transfusion given immediately after the marrow puncture produced a dramatic change in her appearance. Before the transfusion it was a point of bedside discussion whether or not she was icteric; after the transfusion she looked so like the other children in the ward that the question of icterus did not arise.

Her subsequent course is illustrated in Fig. 4. Her platelet count rose within six days to her normal figure, while her reticulocyte count did not rise until several days later.

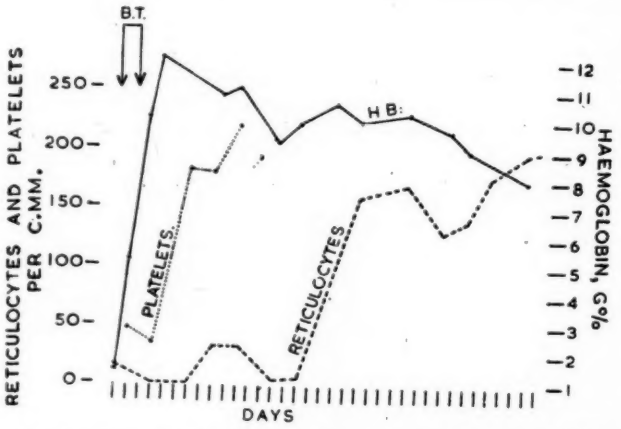

FIG. 4.—Case 3. Showing the changes in reticulocytes, platelets, and haemoglobin during the crisis. Blood transfusions were given at the points marked B.T.

Later marrow studies showed hyperplasia of the erythron (Fig. 5). Bilirubin studies could not be carried out. Her mother's erythrocytes showed increased fragility in saline, but she gave no history of anaemic crises.

After the child's spleen was removed her reticulocytes fell from their apparent usual level of 200,000 to 8,000 per c.mm. Her haemoglobin remained around 14 g.%. She has since then shown no clinical symptoms.

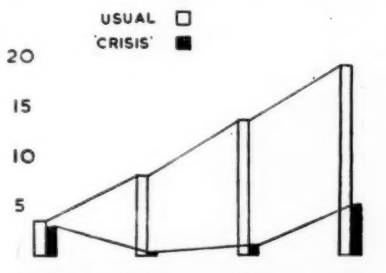

FIG. 5.—Case 3. Showing the percentage of primitive cells of the erythron in the bone marrow during the crisis and after recovery from the crisis.

Comment.—This girl was admitted in a severe anaemic crisis which, but for a blood transfusion, would probably have been fatal. Her severe anaemia clinically unmasked her continually raised serum bilirubin, giving her a mild yellow tinge. After transfusion this disappeared. Her marrow showed extreme hypoplasia of the erythron during the crisis, compared with hyperplasia in her usual state. The return of platelets in her peripheral blood preceded the return of reticulocytes. The latter may have been postponed by the adequate blood transfusion.

Discussion

In the three children described here four crises were seen. All of these crises were associated with a reticulocytopenia in the peripheral blood and a period of hypoplasia of the erythroid element of the bone marrow. In the case most carefully studied the two crises were preceded by a period of symptoms suggesting an infection and both crises resolved spontaneously. The other two cases showed more severe anaemia and required blood transfusion. From a biochemical point of view the one case in which faecal bile elimination was studied showed diminished excretion during the crisis period, and in one other case the blood bilirubin was not significantly raised during the crisis.

Owren (1948), in a study of six cases of crises in acholuric jaundice, saw reticulocytopenia in five of them. In one case he followed the marrow picture through the complete crises. He observed that in the crises the red blood cell count fell to about a half of the original level in about six days. He noted a reduction in serum bilirubin and diminution in urinary urobilin excretion. In the bone marrow he saw a spontaneous recovery of the erythron, beginning on the ninth day of crises. He considered that the aplastic phase of the bone marrow was able of itself to account for the blood changes during the crises. The finding of marrow aplasia during the period of crises was confirmed by Dameshek and Bloom (1948), but they considered the crises to be due to a phase of hypersplenism in which the spleen produced an inhibitory effect on the bone marrow and at the same time itself increased its own haemolytic activity. The aplastic factor in the crises was also confirmed by Gasser (1950), Cremer (1950), and Hermansky (1951). Schrumpf (1950) summarized a group of papers read at the Société Européenne d'Hématologie at Montreux by saying "... it is advised to remove the statement from most textbooks of increased reticulocytic number during haemolytic crises. What really happens is that the number is lowered during the crisis."

It was soon noted that similar aplastic crises occurred in sickle-cell anaemia (Singer, Motulsky, and Wile, 1950; Chernoff and Josephson, 1951). In this condition hypersplenism does not seem to occur and removal of the spleen does not influence the course of the disease.

In discussing the cause of the anaemic crises the most important single factor would seem to be the length of life of the individual cell. It has been shown that whereas the life of a normal red cell is about 100 days that of a red cell in a case of hereditary spherocytosis is about 14 days (Dacie and Mollison, 1943; Owren, 1948). Thus if there was an absolute cessation of red cell production for a period of 10 days in a normal person the effect on the peripheral blood would be a reduction of about 10% of the peripheral count for 100 days. In a case of spherocytosis, on the other hand, a similar cessation of cell production would result in a precipitous fall in red cells. If the aplasia lasted 14 days it would theoretically result in there being no peripheral surviving cells at all. It is this feature which would seem to account for the presence of anaemic crises in spherocytic and sickle-cell anaemia.

Clinically the crises often appear to have a very rapid onset, but this is compatible with the view that the anaemia is due to aplasia. The clinical acute pallor will be associated with a fall of haemoglobin from the regions of 5 g. to around 3 g. This can easily occur owing to the elimination by the spleen of surviving spherocytes in 36 to 48 hours. It is interesting to observe that in Case 1 of our series the two crises were of different severity, the second crisis being much less severe than the first. The milder crisis was associated with a less marked reticulocytopenia.

Three mechanisms that need discussion in the production of the crises are (1) the role of increased haemolysis, (2) hypersplenism, and (3) marrow aplasia.

There is virtually no evidence of increased haemolysis in cases recently studied and reported during crises. No increase in bile excretion occurs. Owren noted an absolute diminution in jaundice and blood bilirubin during the crises. The name "acholuric" attached to the disease is on simple clinical observation that in this type of jaundice an increase in bile elimination does not occur. The theory of two forms of bilirubin used to explain the anomaly is probably false (Gray and Whidborne, 1947).

The role of hypersplenism was largely adopted by Dameshek and Bloom; they had no evidence that the spleen itself produces the marrow aplasia. They noted a relative increase in the number of spherocytes in the peripheral blood during crises and suggested that this was due to splenic activity. A more likely explanation is that in crises there is a relative increase in older and hence spherocytic cells. The presence of aplastic crises in sickle-cell anaemia, in which hypersplenism does not seem to occur, necessitates a different explanation of the crises in the two similar diseases. Further, Freund (1932) refers to cases in which splenectomy did not prevent later death from anaemia.

The evidence suggests that the aplasia of the erythron can itself account for the clinical presentation of an anaemic crisis. In that case why the aplasia ?

It has been considered that the crises in spherocytic anaemia are often precipitated by infection (Murray-Lyon, 1935 ; Scott, 1935 ; Dameshek, 1941 ; Horne, Lederer, Kirkpatrick, and Leys, 1945), and recently it has been recognized that certain infections, notably diphtheria and infectious mononucleosis (Gasser, 1950 ; Chernoff and Josephson, 1951), may be associated with a transient hypoplasia of the erythron.

In spherocytic anaemia we have to consider the effect of an infection upon a bone marrow in a state of prolonged and profound compensatory hypertrophy and therefore especially liable to a conditioned nutritional deficiency. The diversion of essential protein which is thought to be responsible for the anaemia of infection (Cartwright and Wintrobe, 1952), could thus be exaggerated in effect, and a relatively acute deficiency could occur, with resulting aplasia.

Such an explanation would seem to us more likely than the postulation of a hypothetical hypersplenism, and would also account for the apparently increased tendency to crises during pregnancy.

Summary

Four crises in three children with spherocytic haemolytic anaemia were studied.

All crises were associated with reticulocytopenia and with hypoplasia of the erythron in the bone marrow.

Recovery from crises was associated with the reformation of the usual hypertrophic marrow.

No evidence of increased haemolysis was seen in the crises.

It is suggested that the marrow aplasia is the primary cause of the anaemic crises and that the aplasia is due to conditional deficiency states induced by the presence in the body of an infection on a marrow undergoing prolonged compensation hypertrophy.

We are indebted to Dr. T. Colver and Professor R. S. Illingworth, the paediatricians in charge of the cases reported here.

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The C.W.S. Retail Co-operative Society of Manchester was fined £120, with 10 guineas costs, at Hastings, Sussex, on March 18 on five summonses in respect of the condition of premises used for food storage at St. Leonards. The society pleaded guilty to summonses accusing them of (1) failing to provide a sufficient supply of water for persons employed there ; (2) failing to see that the walls, ceilings, and doors of the room had been purified ; (3) failing to give notice that an infestation of rodents was present in the room ; (4) failing to protect food stored in the room ; and (5) failing to see that the walls, ceilings, floors, and windows were kept in a proper state of repair. The premises were used for the storage of cereals, rice, and beans in sacks and packages. A spokesman for the society said they deplored this matter and now had very good premises.

FURTHER TRIAL OF AUREOMYCIN IN THE TREATMENT OF CHOLERA*

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In a previous communication (Seal, Ghosal, and Ghosh, 1951) the results of a preliminary trial of aureomycin, administered intravenously, in the treatment of cholera cases were reported. These being unsatisfactory it was suggested that the oral route might be chosen for the administration of the drug if further trial was undertaken in future. Accordingly a trial was organized in the same institution at Calcutta, this time during the prevalence of cholera epidemic in the city between April 30 and July 20, 1951. Only frankly typical cases were chosen at random and were divided into three groups: experimental, sulphaguanidine control (control 1), and saline control (control 2), the number of cases treated in each group being 50, 35, and 35 respectively, total 120. The subjects were all males and were admitted in a stage of collapse, generally within 24 hours of the onset of symptoms, and had received little or no treatment prior to admission to hospital.

Treatment

Dosage.—The drug was supplied in capsules, each containing 250 mg. In the previous study the dosage used for intravenous administration was 100 mg. every six hours, and in a few cases 50 mg. every three hours, the total quantity used being generally 300 mg. Some untoward symptoms were noted with 100 mg., but not with 50 mg. per adult dose. With this experience, and in the absence of any previous knowledge of the dose which would be suitable for oral administration in cholera patients, it was tentatively decided to try one capsule of 250 mg. every three hours. This amount was easily retained with no untoward effect referable to the drug. A few cases which showed complications during the course of the disease will be discussed later. Of the 43 cases which recovered 8 were clinically severe, 23 moderately severe, and 12 were mild, the average doses received by these groups being 6.65 g., 5.5 g., and 4.875 g. respectively. From the nature of response obtained by oral administration of the drug it appears that 500 mg. every three hours or 250 mg. every one and a half hours may be tried as an initial dose, whichever is found convenient, and if the drug is effective at all the total amount actually needed for recovery may be much less than has been used in the present investigation, perhaps about 3 to 5 g., depending upon the severity.

Other Treatments.—As in the previous trial, all cases brought to the hospital in a state of dehydration and collapse were given intravenous saline and glucose in varying

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†Dr. S. C. Ghosal has died since the paper was written.

doses before the administration of the experimental drug. In severe cases, this treatment was further supplemented by alkaline saline, coramine, and atropine whenever necessary.

Treatment of Controls.—Two groups of control cases were simultaneously treated, one receiving sulphaguanidine in place of aureomycin and the second receiving no specific drug, the " other treatments " being the same in all the three groups. The initial dose of sulphaguanidine was 4 g., the total doses varying from 4 to 36 g. (average 25 g.) in the cases which recovered.

Laboratory Examinations

Examination of Stool Samples.—The procedures adopted by Chaudhuri *et al.* (1950) were followed for the collection and examination of stool samples, and only specimens collected by means of a sterile rectal rubber catheter or on a burnt earthenware vessel and removed to the laboratory in sterile borate-buffered salt solution were accepted for cultural examination. This had twofold advantages. It eliminated the use of a bed-pan, which could give spurious results due to imperfect washing and sterilization or to the presence of some residual antiseptics; secondly, it gave more reliable data about the period of excretion owing to the greater chance of isolating *V. cholerae*, if present, by this method than by others. A case was considered bacteriologically negative when at least three consecutive stool samples inoculated into the enriched medium proved negative to *V. cholerae*. Seventy-five or 62.5% of the patients were vibrio-positive, yielding Inaba type in 64 cases, Ogawa in 10 cases, and both Inaba + Ogawa in one case. The vibrio-positive cases were equally distributed in the three groups (see Table II).

Examination of Blood Samples for Non-protein Nitrogen.—As in the previous trial the examination of blood samples from the cholera patients for non-protein nitrogen was carried out in the Biochemistry Section of the Calcutta Medical College. The estimation could be made only in 28 patients, 12 from the aureomycin group and 8 each from the two control groups; these tests were done mostly in the earlier period of the investigation; the difficulty arose out of the gas-workers' strike in Calcutta during the months of May to July, 1951. The amount and distribution of non-protein nitrogen in different groups of cases, according to the nature of complications, are given in Table I.

TABLE I.—*Amount and Distribution of NPN (mg./100 ml.) in the Blood of Cholera Patients According to the Nature of Complications in Different Experimental Groups.*

Group Treated With	Uraemic Cases		Lung Complication		Tympanitis		Jaundice		Vasomotor Failure		Without Complication	
	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)	No. of Cases	Blood NPN in Cases Tested (mg./100 ml.)
1	2	3	4	5	6	7	8	9	10	11	12	13
Aureomycin	5	95 (D), 86 (D), 60, 38	2	25 (D)	—	—	2	56	—	—	41	15, 16, 20 (D), 22 (D), 39·2, 42
Sulphaguanidine ..	4	90 (D), 72·8 (D), 53	—	—	1	18 (D)	1	—	1	39·2	28	24, 28, 45
Saline ..	1	86 (D)	—	—	1	—	—	—	—	—	33	25, 25, 26 (D), 28, 34, 24, 62 (D)
	10	8	2	1	2	1	3	1	1	1	102	16

The letter D in parentheses stands for death.

TABLE II.—*Showing the Clinical States and Progress of the Three Groups of Cholera Patients Treated with Aureomycin (Oral), Sulphaguanidine, and Saline Respectively.*

Clinical States	Aureomycin (Oral)-treated Group	Sulphaguanidine-treated Group (Control 1)	Saline-treated Group (Control 2)
Number of cases treated	50	35	35
Age distribution (in years)	10–50 (average 30·5 years)	12–60 (average 31·2 years)	14–80 (average 31 years)
Duration of illness before admission (hours)	1½–48[1] (average 9·6 hours)	3½–48[2] (average 15 hours)	4–72[3] (average 17·2 hours)
Sp. gr. of blood on admission	1062 (3), 1062 (14), 1063 (3), 1064 (10), 1065 (3), 1066 (9), 1067 (1), 1068 (7); average 1064·2	1061 (1), 1062 (8), 1063 (1), 1064 (8), 1065 (1), 1066 (11); 1068 (3); average 1064·5*	1062 (7), 1063 (2), 1064 (5), 1065 (4), 1066 (10), 1067 (3), 1068 (4); average 1065
Clinical types	Severe 15 (30%); Mod. 23 (46%); mild 12 (24%)	Severe 8 (22·9%); Mod. 16 (45·7%); mild 11 (31·4%)	Severe 11 (31·4%), Mod. 16 (45·7%); mild 8 (22·9%)
Condition of urine on admission ..	Suppressed 32 (64%); scanty 18 (36%)	Suppressed 16 (45·7%); scanty 19 (54·3%)	Suppressed 19 (54·3%); scanty 16 (45·7%)
Duration of suppression of urine (hours)	6–36 (average 16·0 hours, SD 2·219)	3–34 (average 16·3 hours, SD 2·103)	11–36 (average 22·75 hours, SD 2·207)
Complications	Uraemia 5; lung complications 2; jaundice 2; total 9 (18%)	Uraemia 4; tympanitis 1; vasomotor failure 1; jaundice 1; total 7 (20·0%)	Uraemia 1; tympanitis 1; total 2 (5·7%)
Blood NPN (mg./100 ml.)	Done in 12 patients (15, 16, 20, 22, 25, 38, 39·2; 42, 56, 60, 86, and 95 mg.—average 42·85 mg.)	Done in 8 patients (18, 24, 28, 39·2, 45, 53, 72·8, and 90 mg.—average 46·25 mg.)	Done in 8 patients (25, 24, 25, 26, 28, 34, 62, and 86 mg.—average 38·75 mg.)
Vibrio positive or negative	Vibrio + 31 (62%); Vibrio − 19 (38%); Inaba 27; Ogawa 3; In. + Og. = 1	Vibrio + 22 (63%); Vibrio − 13 (37%); Inaba 20; Ogawa 2	Vibrio + 22 (63%); Vibrio − 13 (37%); Inaba 17; Ogawa 5
Excretion of vibrios (average duration)	2·75 days (SD 0·132)	3·2 days (SD 0·164)	3·72 days (SD 0·271)
Average number of stools during the first 5 days of admission	10·9 (SD 0·919)	12·3 (SD 1·611)	14·1 (SD 1·902)
Average duration of illness (acute stage)	37·1 hours, SD 1·611 (average of 43 cases); 37·4 (including the dead)	39·7 hours, SD 2·249 (average of 29 cases); 39 hours (including the dead)	47·3, SD 3·530 (average of 29 cases) 43 hours (including the dead)
Average amount of saline used (pints)	6·0 (average of all cases); 5·96 (excluding the dead)	6·0 (average of all cases); 5·7 (excluding the dead)	6·2 (average of 34 cases); 6·3 (excluding the dead)
Specific drugs	4 to 36 capsules (250 mg. each); average 23 capsules (excluding dead)	4–36 g.; average 26 g. (excluding the dead)	Nil
Number died	7† (14·0%)	5 (14·3%)	5 (14·3%)
Period between admission and death or cessation of acute stage	28·3 hours (excluding the dead); 28·8 hours (all cases)	28·0 hours (excluding the dead); 28·4 hours (all cases)	30 hours (excluding the dead); 27·2 hours (all cases)
Average length of stay in hospital (days)	5·5 (excluding the dead); 6·2 (all cases)	6·5 (excluding the dead); 6·2 (all cases)	5·9 (excluding the dead); 6·8 (all cases)

* Sp. gr. of two cases not estimated.

† One case had only 1 capsule and died within 3 hours of admission and another had 2 capsules and died within 4 hours of admission. Fatality rate excluding the first case = 12·2%.

[1] 48 hours—1 case; [2] 48 hours—3 cases; [3] 48 hours—3 cases, and 72 hours—1 case.

Reactions after Oral Administration of Aureomycin

Five cases in the aureomycin-treated group developed uraemia, two cases lung complications, and two cases jaundice, total nine cases (18%). Similarly in the sulphaguanidine-treated group four cases developed uraemia, one case tympanitis, one case vasomotor failure, and one case jaundice with pain in the abdomen, total seven cases (20%). In contrast with this only two cases (5.7%) in the saline-treated group showed complications. It is thus a question whether these complications were in any way the results of drug treatment. Though the appearance of jaundice in two cases and uraemia in five cases treated with aureomycin may be considered as some evidence for the toxic action of the drug it is doubtful whether the latter was directly responsible for the complications : not only did the amounts of the drug administered to the patients who developed complications vary widely—namely, 1, 1.75, 4.5, 4.75, and 7.25 g. in the uraemic cases, 3.5 and 4.75 g. in the jaundiced cases, and 5.25 and 6 g. in cases with lung complications—but also all those who received as much as 9 g. each (two severe, three moderate, and one mild), recovered without any complication. This question will be discussed again later.

Results

The data relating to the clinical states and the progress of the patients in the aureomycin-, sulphaguanidine-, and saline-treated groups are summarized in Table II. As will be seen, the cases in the three groups are fairly well distributed in regard to age, clinical stage at the time of admission, specific gravity of blood, condition of urine, and positive isolation of *V. cholerae*. In so far as the end-results are concerned there is no appreciable difference between the three methods of treatment, but in regard to certain minor points aureomycin treatment showed some advantages.

Unlike the previous trial by the intravenous route the blood non-protein nitrogen was generally within the normal range in the majority of cases treated by aureomycin, being high only in two of the twelve cases examined. The same was true of the control groups. The average duration of the suppression of urine in the aureomycin group was significantly less than that of the saline-treated group by 6.8 hours ($t=2.099$ with 41 d.f., as against 2.021 with 40 d.f. at 5% point of t), but there was very little difference between the aureomycin and the sulphaguanidine groups in this respect ($t=0.105$ with 39 d.f. and 90% point of t with 40 d.f.$=0.126$).

So far as complications, such as uraemia, lung symptoms, jaundice, and tympanitis, are concerned, the advantage was definitely in favour of the saline controls, there being hardly any difference between the aureomycin and the sulphaguanidine groups. However, a significant advantage of the aureomycin group over the saline controls is found in respect of the duration of excretion of vibrios. Although the difference is small it is statistically significant ($t=3.514$ with 43 d.f., as against 3.551 with the same d.f. at 0.1% point of t). The same advantage is found over the sulphaguanidine group ($t=2.417$ with 45 d.f. and 2% and 5% point of t with the same d.f. are 2.423 and 2.021 respectively). Similarly the average duration of the acute stage was curtailed by 10 hours in the aureomycin group compared to the saline group ($t=2.919$ with 69 d.f. and 1% point of t with 60 d.f. $=2.660$). In this respect the sulphaguanidine group gave nearly the same results as the aureomycin group. The average number of stools during the first five days of hospital treatment was also less in the aureomycin-treated group than in the sulphaguanidine- or the saline-treated group, though the difference is not statistically significant. Some difference was also noted in the average length of stay in hospital of patients in the three groups, the advantage being in favour of the aureomycin group, but the discharge of the patients from the hospital was not strictly guided by the condition of the patient. There was no difference, however, in the fatality rates of the three groups of patients.

Comments

Although no appreciable reduction in the fatality rate of patients treated with oral aureomycin was obtained, the findings of this investigation are nevertheless interesting. Firstly, the toxicity seen after intravenous administration was practically eliminated, the toxicity being no greater than was observed in the cases treated with sulphaguanidine. It is true, complications were much less without any chemotherapy, but treatment with aureomycin had certain advantages. For instance, there was a significant reduction in the average period of suppression of urine as well as of the acute stage of the disease. Perhaps more important than this, from the point of view of epidemiology and international quarantine laws, is the fact that the patients became vibrio-free earlier than with sulphaguanidine or saline treatment. However, judging from the fatality rates and from the average amount of saline used in each group it is difficult to avoid the impression that the drug had no influence upon the course of the disease. This would appear to support Lahiri's (1951) view that no specific drug has yet been found in cholera. We do not, however, fully subscribe to this. In the experience of one of us (S. C. S.) in the field trial of sulphaguanidine (Seal, 1947) it became quite clear that the secret of success in the treatment of cholera cases lay in their early treatment ; once dehydration and collapse set in, the administration of a vibrio-static drug is of no help without saline treatment ; and treatment with a vibriocidal drug becomes sometimes positively harmful owing to the release of a large quantity of endotoxin at a stage when the patient is already at a serious disadvantage owing to the extreme loss of fluid.

Another difficulty is the great individual variation in the behaviour of patients against cholera infection. Some people are more apt to develop vasomotor failure or uraemic symptoms than others, and such cases generally do not respond easily to treatment. Again, the fatalities mostly occur in the earlier part of the epidemic and there is proportionately greater chance of recovery in cases occurring after the peak period. Thus, in the present study, deaths in all the three groups occurred during the first two weeks of May, 1951—that is, the early weeks of this investigation. In fact no fatality occurred amongst 35 patients treated with another antibiotic during the period between May 22 to July 18, 1951. The failure of any drug in the advanced stages of cholera does not necessarily mean that it has no action on the cholera vibrio. Aureomycin is vibriocidal *in vitro*, and the quicker disappearance of the organism from the convalescent cases indicates that the drug is also effective *in vivo*. The dose of aureomycin capsules used in the present investigation was probably high. A lower dose of 3 to 5 g. according to the stage of the disease may be found sufficient.

Summary

1. In a trial of oral aureomycin for the treatment of cholera, 50 patients were treated with aureomycin capsules, 35 with sulphaguanidine, and 35 with saline, the last two groups acting as controls.

2. There was no difference in the fatality rates among the three groups, which were all about 14%. In the group receiving aureomycin the acute stage was shorter, and the duration of suppression of urine and the period of excretion of vibrios were reduced. There were no serious toxic effects.

3. The results are discussed.

Thanks are due to Dr. A. K. Dutta Gupta, Principal, Nilratan Sircar Medical College, for kindly providing facilities for this investigation and to Dr. M. Chakrabarti, Professor of Physiology, Medical College, Calcutta, for carrying out the blood examinations for the estimation of N.P.N.

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Medical Memorandum

Spontaneous Perforation of the Colon Due to Alkaline Medication

The following case is reported because, although it is almost unique, it results from a very common combination of circumstances.

CASE REPORT

A man aged 68 was admitted to hospital complaining of severe lower abdominal pain. He had been investigated in another hospital six months previously because a duodenal ulcer was suspected, but a barium meal examination did not confirm this. Subsequently he had taken an unidentified alkaline preparation. On the morning of March 4, 1950, he paid a routine visit to his doctor. There he collapsed with severe lower abdominal pain which led to his admission to hospital. He gave a history of increasing constipation during the previous few months with occasional bleeding at stool.

Examination showed an old man with evidence of recent weight loss. There was a slight degree of shock with cold extremities and perspiration. The temperature was 96.8° F. (36° C.), pulse 66, respirations 20, and blood pressure 140/95. The lower abdomen was very tender, with muscle spasm almost amounting to rigidity. Rectal examination showed the bowel to be full of large hard faecal masses. Immediate laparotomy was advised, though it was some hours before the patient would consent to this.

Under general anaesthesia the abdomen was opened through a right lower paramedian incision. There was a moderate quantity of turbid fluid with a faecal odour in the peritoneal cavity. In the pelvic colon there was a perforation about 1 cm. across on the antimesenteric border. Around its edges was a ring of necrotic tissue about 1 mm. in width. Through the perforation a hard faecalith was protruding. This proved to be a very hard spherical whitish lump of faeces with a rough gritty surface. Palpation showed the whole of the descending and pelvic colon and the rectum to be full of similar material. The perforation was temporarily closed by suture, and the loop in which it lay was then exteriorized through a separate incision in the left iliac region, where it was fixed by passing a glass rod through its mesentery. The temporary suture was then removed so that the perforation became a colostomy opening. Exteriorization was performed under some tension owing to the shortness of the mesosigmoid. The abdomen was closed with drainage of the pelvis.

Intravenous fluids were given and gastric aspiration was continued for four days, and streptomycin, 1 g. twice daily, was administered. The patient progressed satisfactorily until the eighth day, when there was a small secondary haemorrhage from the colostomy, possibly due to the tension of the colon over the glass rod. Bleeding recurred and was fatal on the eleventh day.

Post-mortem examination confirmed the operation findings. In particular, the colon, both throughout its length and at the site of perforation, was normal. The condition was a perforation of an acute stercoral ulcer due to faecal impaction, presumably caused by alkaline medication, and occurring in an otherwise normal colon.

DISCUSSION

Spontaneous perforation of the colon—that is, perforation not due to external injury—is familiar to all surgeons with experience of abdominal emergencies. In discussing the aetiology, apart from malignant disease, Koucky and Beck (1940) mention diverticulitis, foreign bodies, enemata, compressed air, tuberculous ulceration, ulcerative colitis, typhoid, and dysentery, to which may be added simple ulcer of the ascending colon (Wilkie, 1937). Woodruff's 1952 review, apart from mentioning Brown's (1944) case, described below, adds no new predisposing cause to these.

Spontaneous perforation of the colon in the absence of any of these factors is very rare. The only cases at all similar to the present one are those of Brown (1944) and of Hoffert (1946). Brown's patient was a man of 30. A few minutes after rising he had a sudden abdominal pain of great severity. On admission to hospital he was shocked and had the signs of generalized peritonitis. At operation the abdomen contained thin turbid fluid. "In the pelvis was a small quantity of faeces. On the antimesenteric border of the pelvic colon close to the pelvi-rectal junction there was a laceration in the long axis of the bowel about 1 cm. long and with a mass of faeces protruding through it. The edges of the laceration were irregular and the bowel wall, apart from involvement in the general inflammation, was macroscopically normal." This patient recovered, and subsequent radiological examination failed to show any evidence of diverticula or foreign body. Brown was unable at that time to trace any similar case in the literature.

Hoffert's case, described two years later, is very similar to Brown's and almost identical with the case now reported. A male patient aged 63 was receiving treatment for duodenal ulcer. He developed signs of peritonitis, and *x*-ray examination showed free gas in the abdomen. At operation there were solid faeces throughout the left half of the transverse colon and descending colon. Two faecal balls were lying in the pelvis and there was a 2-cm. perforation in the sigmoid. This patient survived following a Paul–Mikulicz resection of the segment containing the perforation.

These two cases and the present one are remarkable in that the perforation occurred in a normal colon and in the absence of trauma. The mechanism of perforation in Brown's case is unexplained, but the fact that the patient was being treated for duodenal ulcer in the other two cases points to a previously unrecognized danger of alkaline medication. The site of the perforation on the antimesenteric wall in two of the cases suggests that this type of perforation is due to impaction of faeces causing tension gangrene, which appears first at that part of the wall with the poorest blood supply. Constipation is a well-known complication of certain alkaline powders, especially bismuth salts and aluminium hydroxide, and patients who have had these medicines prior to partial gastrectomy often develop post-operative diarrhoea due to faecal impaction in the rectum, a complication which may also occur if operation follows soon after a barium meal.

Even without the interruption of rectal function which follows an operation, old and constipated patients may develop faecal impaction while receiving alkaline powders, as another recent personal case shows. Hunt (1950) says: "Aluminium hydroxide and aluminium silicate are constipating and tend to produce dry hard stools with, in some cases, even troublesome faecal impaction. Magnesium trisilicate, on the other hand, in sufficient dosage to be effective in relieving pain is laxative and irritant to the intestine, so that colic borborygmi and intestinal flatulence make it difficult to use. A mixture of these two is rational . . . and probably the best of the antacids available."

The same principle is already familiar in the balancing of bismuth and magnesia in the older powders. Although this stasis seldom leads to perforation of the colon, minor degrees of impaction, irritation, and even ulceration are probably quite common. It is suggested, therefore, that if alkaline powders play any part at all in the treatment of peptic ulcer the two substances mentioned should be combined with liquid paraffin and a mild aperient (a combination likely to reduce calcium intake); or, better, an alkali which has a mild aperient action, such as magnesium carbonate or trisilicate, should be included in the mixture.

I wish to thank Mr. J. B. Oldham for help and advice in the preparation of this paper.

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Reviews

PRINCIPLES OF PUBLIC HEALTH

The Health of the Community: Principles of Public Health for Practitioners and Students. By C. Fraser Brockington, M.A., M.D., D.P.H., B.Chir.(Cantab.), M.R.C.S.(Eng.), L.R.C.P.(Lond.). With a foreword by Sir John Stopford, M.D., Sc.D., LL.D., F.R.C.P., F.R.S. (Pp. 415. 32s.) London: J. and A. Churchill Ltd. 1954.

This is a well-written and timely book. Professor Brockington has wide experience of the public health service and has maintained over the years a close interest in academic teaching and field research. This book has the great quality of being a personal document. Although much of his material is highly compressed, he never hesitates to use vivid illustrations from his own experience. In fact this is a first-rate example of how to write a short book on a large subject without making it synoptic and dull. It is vivid and interesting, comprehending much in few words. Professor Brockington handles figures with ease, and he might have been tempted to produce acres of tables; instead of this he weaves the figures into the pattern of the story in such a way as to add to their interest. He goes a step further indeed: "The use of numbers in epidemiology," he says wisely, "(and in a book about people) is unavoidable, and, although they may at first sight seem to be impersonal and lacking in human qualities, to those who come to understand them figures are in reality as full of meaning and poignancy as any descriptive writing; each is the record of a human life and in the aggregate of groups of people or of the whole nation."

He is not afraid of verbal imagery even when he is using words with the utmost economy. In discussing mental ill-health, for example, he says, "A large fraction of the time and energy of the State is concerned to cope with the end results—hospitals, institutions, clinics, home care, and supervision; the operation of courts of law in crime, delinquency, and divorce; the problem of absenteeism from work—yet this may be proportionately not more than the visible part of an iceberg is to the whole floating mass." Sometimes the compression is too great, and a comma or two become displaced, with curious results. The reader may be a little startled by the remark about medical officers of health: "He cannot like his colleague, the family doctor . . ." until he discovers that the sentence is governed by what follows: "apply whatever treatment he thinks appropriate."

This book is an admirable statement of principles and the author never loses sight of his main objects. He may be a trifle optimistic about the future unification of the health services, but he states his case cogently and shows evidence of a deep understanding of the position as a whole. He restates with great skill and restraint the scope and functions of the medical officer of health, and does battle valiantly to secure the general practitioner in his rightful place. This book should be read by all who are interested in the development of the public health service and particularly in the health of the community in its broadest sense. The blemishes are trivial in a book at once so interesting and comprehensive.

J. M. MACKINTOSH.

GENERAL PRACTITIONERS' SYMPOSIUM

Clinical Medicine in General Practice. Edited by John Fry, M.B., B.S., F.R.C.S. With a foreword by Sir Henry Cohen, M.D., D.Sc., LL.D., F.R.C.P. (Pp. 436. 27s. 6d.) London: J. and A. Churchill Ltd. 1954.

This book is a symposium by eight general practitioners and edited by Dr. J. Fry. The first chapters describe the management of a practice and the work done by rural and urban practitioners. Chapters on cardiovascular diseases (Dr. C. Papp), rheumatic disorders (Dr. A. Talbot Rogers), and the common fevers (Dr. G. O. Barber) are written by experts who are good teachers as well as general practitioners. The reader's enjoyment is slighty marred by some tiresome misprints in the chapter on rheumatic disorders. It appears that clinical medicine in general practice is based on the same principles as in hospital practice. It is stressed that the general practitioner has special difficulties and responsibilities because he is the first to see the patient and has to distinguish between the trivial and the serious.

Dr. Watts, writing on nervous disorders, insists on the importance of diagnosis. He cuts a path clean through the jungle of psychological undergrowth that besets the general practitioner. One can but marvel at his ability to label his specimens so neatly. It seems too good to be true. Writing on obstetrics he is disappointing. He repeats the hospital teaching on antenatal care, including a fearful pamphlet handed to the expectant mother, and believes the general practitioner's chief function in a normal confinement is to act as anaesthetist to the midwife.

Dr. Fry on respiratory diseases nicely illustrates how a general practitioner is able to take the long view of his patients' disorders. His description of the development of bronchitis and emphysema in a patient over twenty years is of great interest, but he commits the error of dividing the respiratory tract into upper and lower. Nowhere is it mentioned that this particular patient had his nasal sinuses *x*-rayed. Dr. Fry and Dr. Pinsent on skin disorders and Dr. Barber on drugs in general practice show that treatment can be rational and yet simple and inexpensive.

The general practitioner is seen at his best in two chapters on children (Dr. Lindsey W. Batten) and the aged and incurable (Dr. Finer). Dr. Lindsey Batten in particular happily combines a scientifically detached attitude of mind to the problem with a really imaginative sympathy with the child—and his mother. If he is not already teaching medical students he certainly should.

This is an uneven book. It is, however, a laudable attempt to show how the general practitioner can be of value to clinical medicine.

C. W. WALKER.

SYNOPSIS OF CHILDREN'S DISEASES

A Synopsis of Children's Diseases. By John Rendle-Short, M.A., M.B.(Cantab), M.R.C.P., D.C.H. (Pp. 620; illustrated. 32s. 6d.) Bristol: John Wright and Sons Ltd. 1954.

Now that paediatrics has become recognized in many universities as a fourth major subject, equal in importance to medicine, surgery, and obstetrics, it is both fitting and timely that a companion volume to Tidy's *Medicine*, Wakeley's *Surgery*, and Bourne's *Obstetrics* should appear in this outstanding synopsis series. This newcomer is particularly welcome, for there is no volume of comparable size available for final-year students revising their paediatrics, or for D.C.H. or M.R.C.P. candidates, and the standard of the contents is admirably suited to these ends. *A Synopsis of Children's Diseases*, which might perhaps better have been entitled "Synopsis of Paediatrics," is a courageous attempt to follow in the steps of the three other masters.

Inevitably a first edition such as this must invite some criticisms, but these are slight. There are commendably few errors and the text is remarkably up to date. Although the author says in the preface that the book is intended for paediatric house-physicians and general practitioners as well as for examination candidates, the details of treatment are, in the main, too sketchy to be of value to residents and general practitioners. The most helpful section, perhaps, is that on diseases of the respiratory system. There are twenty-one tables of differential diagnosis, and these will prove most useful. It is a pity, however, that one of these is devoted to the differentiation between mongolism and cretinism, although this is following tradition. Mongols and cretins are so unlike, and each has such distinguishing characteristics, that there should be no need for this table in future editions.

There is one severe criticism—and that is the use of "etc." This appears—usually more than once—on almost every one of the 554 pages encompassing the 174 chapters. And it is a very bad example to examinees. The height of synopsis is reached in Chapter 168, which reads: "Gonorrhoea. In girls—see p. 393. In boys—very rare. Signs, symptoms and

treatment etc. as for adults." Why the etc.? On page 150, in the indications for tonsillectomy, no mention is made of the importance of enlargement of the tonsillar glands. On page 220, in the treatment of Hirschsprung's disease, ephedrine sulphate 2 gr. is the dose recommended. As no reference is made to the age of the child so to be treated this is certainly a dangerous recommendation.

This is really a most valuable book and is certain of a wide circulation.

WILFRID GAISFORD.

THE CHRISTIE CASE

Medical and Scientific Investigations in the Christie Case. By Francis E. Camps, M.D. Foreword by the Attorney-General, Sir Lionel Heald, Q.C., M.P. (Pp. 244; with 47 diagrams and photographs and 6 coloured plates. 30s.) London: Medical Publications Limited. 1953.

The case of John Reginald Halliday Christie was unusual in several respects, but especially because of the number of women who died from violence in one house. That the details of medico-legal investigation adopted in such cases should be recorded is of high importance for reference and other purposes. In this monograph the story of the finding of the bodies and the ensuing scientific and police investigations, together with the medical evidence, are fully explained. It is a welcome addition to volumes which have already treated similar subjects. Throughout the text and in many illustrations the methods used are fully described. The reader cannot fail to be impressed by the scrupulous care taken by the investigators not only in the collection but in the evaluation of the evidence.

In this case, as in others within recent times, the anatomist plays a predominant part. The appendix to the book, in which the methods of estimating stature from long bones are not only fully described but compared, is of very considerable value to all whose work is concerned with such an undertaking. The formulae devised by Karl Pearson, Dupertuis and Hadden, and Trotter and Gleser are discussed and their comparison illustrated by their application to five subjects. The author indicates that the Pearson formulae underestimate the true height and that those of Trotter and Gleser give the best results. In this work Dr. Camps has received the able assistance of Dr. Richard J. Harrison, reader in anatomy, University of London, and of Professor A. E. W. Miles, professor of dental pathology, University of London, and of others.

Throughout the text the findings are carefully described, and, more important still, the methods whereby the results were obtained are recorded. This record will be of benefit in any future similar investigation. To the medico-legal consultant, pathologist, police surgeon, lawyer, and indeed to all concerned with medico-legal problems this volume will prove of high value. The author and his collaborators are to be congratulated. The illustrations are numerous and well produced and the production is of a high standard, for which the publishers should be complimented.

J. GLAISTER.

RADIOLOGY OF BONE DISEASES

The Radiology of Bones and Joints: An Introduction to the Study of Tumours and other Diseases of Bone. By James F. Brailsford, M.D., Ph.D., F.R.C.P., F.I.C.S.(Hon.). Fifth edition. (Pp. 875; over 725 illustrations. 90s.) London: J. and A. Churchill. 1953.

Radiology, though still a young branch of medicine, is now sufficiently mature to span easily a man's whole professional life. This point cannot be better illustrated than by reference to the book under review. In the preface to the new edition the author writes: "The book now comprises a digest of the work of the author since he was appointed to the staff of the Pathological Department of the University of Birmingham forty-six years ago." The work has grown in size and maturity concurrently with the experience of the writer. The first edition was published in 1934, and this one, the fifth, is about twice as long and contains about twice as many illustrations.

The general structure has changed but little since the last edition five years ago. Rather more space has been devoted to bone tumours, the problem perhaps of greatest interest to the author and that to which he has made his most important contributions. On this theme he has always been stimulating and provocative. There are probably few more worrying problems in the whole of medicine than the accurate diagnosis and correct treatment of bone tumours. Classical medical teaching leads us to rely on the veracity of histological reports, but we are liable to become disillusioned if the subject is a possible bone tumour. When three expert pathologists all differ in their opinion—as can happen—on one section, and when each may ultimately be proved to be wrong, a strong case can be made out for the expert bone radiologist having a casting vote. Dr. Brailsford has done much to reorientate our views in this respect, and for that alone his name would be important. Bone tumours are likely long to remain difficult diagnostic problems, partly because they are sufficiently rare for more than a few to gain sufficient experience to develop a mature judgment.

Brailsford's work is too well known, not only to the English-speaking world, but also to the Spanish, into which language it has been translated, to require further comment. It is a pleasure to see that first-class paper is now being used again so that the blocks may be reproduced to their best advantage, so important particularly for bone lesions.

J. W. D. BULL.

THE NATIONAL HOSPITAL

The National Hospital, Queen Square: 1860–1948. By Gordon Holmes, M.D., F.R.S. Foreword by Sir Ernest Gowers, G.C.B., G.B.E. (Pp. 98; illustrated. 10s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1954.

The introduction of the National Health Service marked the end of an epoch, and has naturally led to the recording in book form of the past histories of many of those hospitals which won international fame while still on a voluntary basis. In this well-produced and readable book Sir Gordon Holmes has written the story of the National Hospital, Queen Square, of which he himself has been such a distinguished ornament. The National Hospital was not only the first hospital to be established solely for the treatment of nervous diseases, but for many years it was, and we believe it still is, the leading centre for neurological teaching and research.

It began in a small way. Miss Johanna Chandler, finding that it was difficult to obtain hospital treatment for paralysed persons, determined to remedy the deficiency, and, though not wealthy herself, by her persistent efforts succeeded in getting such a hospital established. It started with only 12 beds, but it filled a need and inevitably grew in size and importance. At present it has about 200 beds and splendid out-patient and research departments. It is in addition a great centre of teaching as a postgraduate school and is recognized as a unit of the University of London.

The author has inserted short biographies of all the chief physicians and surgeons who have been associated with the hospital in the past and are no longer living, and these impress one with the large proportion of truly distinguished men who have worked there. It is an inspiring story, and these great men are not likely to be forgotten. We hope also that the memory of Miss Johanna Chandler will be kept alive.

ZACHARY COPE.

In *Medicine in Oxford* (Basil Blackwell, 10s. 6d.) Dr. Maurice Davidson discourses pleasantly on the general history of the University of Oxford, emphasizing those events and statutes that specially affected the development of the medical curriculum. He draws attention to the "Laudian code" of 1636 and sympathetically portrays the personality of Archbishop Laud (1573–1644). A particular feature of these FitzPatrick Lectures, delivered before the Royal College of Physicians of London in 1952–3, is the very fine series of portraits. The book should be a useful companion to H. M. Sinclair and Robb-Smith's *History of Anatomical Teaching in Oxford*, Oxford, 1950.

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GOOD GENERAL PRACTICE

This week the Nuffield Provincial Hospitals Trust publishes in book form a report[1] by Dr. Stephen Taylor of a survey of 30 general practices in England and Wales. This survey was commissioned three years ago "at a time," as the foreword of the report says, "when there was not perhaps as sympathetic an attitude as now seems usual towards the problems and opportunities of general practice." The survey was to be non-statistical and, also in contradistinction to that carried out by Dr. S. Hadfield on behalf of the B.M.A.,[2] not of a random sample of practices but of a selected number of good practices. The whole purpose of the report is, in a sense, an attempt to define and describe good practice, and therefore those practices were chosen which were generally regarded by other practitioners as outstanding. It is encouraging to read that such practices proved "surprisingly easy to find." In the 30 practices there were 94 doctors, of whom 81 were principals and 13 were assistants. Dr. Taylor was guided in his investigation by a steering committee under Sir Wilson Jameson with Dr. G. Barber, Sir Ernest Rock Carling, Sir Henry Cohen, Mr. Leslie Farrer-Brown, Dr. J. Revans, Dr. A. Talbot Rogers, and Sir James Spence as members. This was an active body, and though the observations in the report are those of an individual the conclusions drawn from them are not.

Surveying the pattern of general practice, the report comes down firmly in favour of the capitation method of payment. It is said that it avoids the disadvantages of both salary and fee for service in a type of occupation where "checking of work done is undesirable and indeed impossible"; and, again, "the independence of mind and spirit of the G.P.s visited has been a striking feature . . . in substantial measure, this appears . . . to be associated with payment by capitation fee." As might be expected, a notable difference in the amount of work per patient per year and in the daily volume of work per doctor was observed in the practices surveyed—variations as great as 3.5 to 9.6 items of service per patient per year and 24 to 87 items of service per doctor per day. "On a basis of general observation" it appeared to Dr. Taylor that fatigue and decline in efficiency started to show itself in the surgery after 15 to 20 patients had been seen and on the round after 10 to 15 visits. From this it is estimated that the average number of services a day should be between 40 and 55, and, on the assumption of an average of 5.3 services per patient per year, this suggests that the "average optimal maximum list is between 2,500 and 3,000."

Of the practices visited in the survey, fourteen had three or more members, and of these fourteen ten were conducted from a single practice house and thus fulfilled what is taken as one of the main criteria of a true group practice. The making of a group practice, its advantages and disadvantages, and the details of its administration are carefully examined. While acknowledging that there are many first-class individual practices and partnerships Dr. Taylor gained the impression that doctors in a successful group almost always supply a better medical service than they would if dispersed. Defining a health centre as "a building where general practitioners carry out their work under the same roof as the local authority clinics" the report goes on to say that there is no point in providing health centres for the sake of any abstract dogma. Policy must be adapted to the nature of the need in areas of different types. Where there are keen and competent general practitioners who undertake maternity and infant welfare work there is a diminishing need for clinics, and to build expensive health centres would be foolish. Where there are good clinic buildings actively at work the report says that it is clearly unnecessary to replace them by new health centres. In such places, mainly industrial areas, it is thought that the need is for group practice buildings and for functional links between the general practitioners and the clinics. Where, however, both the clinic buildings and the general practitioners' premises are poor or non-existent, such as the new towns and housing estates, the case for building health centres is strong.

The section devoted to the thorny problem of the general practitioner's place in hospital work will be read with special interest. It is suggested that the development of clinical assistant posts on the widest possible scale is likely to become the key to the whole problem, provided that these posts are regarded as training appointments and as a means of forging personal links between general practitioners and the local specialists and hospitals rather than as an easy way of supplying an extra pair of hands to the hospital. Of general-practitioner beds the experience in the survey suggests that, where general practitioners have

[1] *Good General Practice*, 1954, Oxford University Press, London.
[2] *British Medical Journal*, 1953, 2, 683.

their own beds available and a general hospital with full specialist staff, the use made of general-practitioner beds is very small. From this comes the conclusion that instead of increasing the number of general-practitioner beds where specialist services exist it would be better to improve the facilities for domiciliary care—by increasing, for instance, the home-nursing and home-help services, and through housing policy. But, the report adds, there is no reason why the general practitioner should not look after his own maternity cases in hospital or nursing-home beds. Almost every general practitioner should regard obstetrics as completely within his sphere. The specialist must be prepared to leave normal midwifery to the general practitioner (except for the training of midwives), and general practitioners on their side must be ready to call in the specialist whenever the need arises. No evidence of anything but good relations between the midwives and general practitioners was found in the course of the survey. Arrangements for normal deliveries, on the whole, were found to be good, and there were several examples of excellent co-operation during the antenatal period. Of the health visitor, it is said that if she is to make a useful contribution towards the care of the general sick in the home as well as of mothers and children she must take her instructions from the general practitioner. No systematic attempt was made in the survey to take evidence from medical officers of health, and any picture gained of the local authority health service was seen through the eyes of the general practitioners interviewed. Criticism of the medical officer of health was less common than complete ignorance of him and all his works, but in one county borough general practitioners and the medical officer of health had set up a joint liaison committee. The report considers that this sort of thing can prove successful, but the initiative for co-operation must come from the medical officer of health.

These are but samples of some of the matters dealt with in considerable detail in a long report on the vast and ever topical subject of the day-to-day work of the general practitioner. A whole chapter and an appendix, for instance, are given to a favourable description of rota systems. Much useful information is given about the use of ancillary help and the planning of the surgery accommodation, and about the scope of the general practitioner's work, together with a section on laboratory work in general practice. The report concludes with an attempt to foretell the future. Remarking that medically the greatest change brought about by the National Health Service has been the diffusion of salaried specialists throughout the country, with a resulting new homogeneity in general practice, it says that "almost all general practitioners must now make domiciliary and consulting-room medicine their primary activity." A future "rich with opportunity" for general practice is envisaged. Open access to the laboratory, to much of the *x*-ray department, and perhaps to some physiotherapy will enlarge the scope of practice. Within the past fifteen years, it is pointed out, technical advances have so greatly extended that to-day the general practitioner in the gloomiest slum practice can treat pneumonia more effectively than most specialists were able to do before the war. "What has happened once," the report says, "may surely happen again." A society which is changing with increasing speed, and against which the future of general practice must be set, in itself will present new problems and growing points, which will, as the report foresees, occupy the general practitioner to the extent that he has the time, energy, and initiative to cope with them. Of the risks to the future of general practice three are singled out. First, that the general practitioner may become lazy in his work. Next, that he may become a relatively unimportant outpost of the hospital service: this risk is a predisposing cause of the first, and many have seen it as the gravest danger to general practice. Lastly, there is the risk to personal freedom and personal integrity which is liable to develop inside any large-scale organization. It is noticeable that nowhere in the report are administrative details discussed. This is in keeping with the attitude of mind with which the survey was approached—namely, that good general practice begins with the good general practitioner and that its quality depends upon the men and women who are actually doing the job. Organization is described as a means to the end of bringing together those who are sick and those specially trained to help them. Beyond this, organization must not be exalted, for this is the way to a tyranny all the more dangerous because it is cloaked with good intentions. The future safety of the doctor's freedom, as the report sees it, lies in his own hands. By their standards of work general practitioners must deserve to be free—"that is the challenge to general practice to-day."

The declared function of the Nuffield Trust is not to pronounce policies but to make accurate experimental studies of various aspects of the health services so that all concerned may benefit. This report fulfils the traditions of the Trust, and, one may add, is a tribute to the tradition of the branch of medicine which it sets out to describe. It is not always clear which conclusions are based on the observations of the practices surveyed and which come from the

consideration of other evidence or from the opinions of the steering committee itself. However, this need not detract from the value of an important document which starts with certain assumptions and then by every means possible sets out to find if these were true or false. Taken in conjunction with Dr. Hadfield's survey, to which in many important respects it is complementary and in broad agreement, this latest Nuffield Report will do much to restore confidence in the future of general practice and is likely to achieve the author's hope that many, particularly the young practitioner, may profit from it. It is a report which all general practitioners should read and digest.

ADOLESCENCE

The period of adolescence is one fraught with immense importance for the individual lad and for the community. It is a period of instability, of development and transition, physical and psychological. There is good reason why this period of change should be beset with difficulty for the young people concerned, striving as they are to adapt themselves to the new freedom—and the new restrictions—inherent in the change from school to employment, facing a host of new interests and new temptations, groping for new values, and all the while developing personality. The approach to youth problems in the depressed years of the 'thirties was inevitably overshadowed by the spectre of unemployment. Cameron[1] and his co-workers found that under the circumstances of those times demoralization was at its worst among young adults of poor social background, and they considered that irretrievable damage had often already been done during the first few years after leaving school. Morgan,[2] in a report to King George's Jubilee Trust, concluded that the voluntary youth movement had so clearly demonstrated the necessities and the possibilities of providing creative leisure activities for youth that its work must go on. "The vague clamour for national fitness," he wrote, "will have meaning when the nation as a whole grasps the fact that only on the bedrock of youth can we lay the foundations of real national fitness." Is it more difficult now for a youth to pass successfully from boyhood to manhood than it was a generation ago? In some ways it probably is; for, while it has never been easier for the school-leaver to step into a comparatively well-paid job, it is equally certain that many of the jobs so readily available are bad, gilded with a thin veneer of apparent attractiveness. Two important new factors have been introduced: one, the raising of the minimum school-leaving age to 15; the other, the introduction of compulsory National Service. The motives behind the raising of the school-leaving age a few years ago were wholly benevolent, but there appears to be some room for doubt whether facilities yet exist in all parts of the country to provide an attractive and useful training for the young people thus kept at school for a further year. For some of them retention at school may be little more than an unsatisfying frustration. Of the introduction of compulsory National Service it may be argued that Service training and discipline will have a steadying value in a period so often characterized by instability; on the other hand, Service life may be a disturbing influence, possibly aggravating the insecurity of adolescence and deterring youth from settling down to a career. There is not yet available any reliable body of evidence on the subject—an extraordinary deficiency, which should surely be remedied.

The transition from school to industry offers at once new problems to the lad and immense opportunities to the sociologist. Osler deplored the attitude of his day which surrounded the child with protective care, only to throw him, on leaving school, more or less by chance into a maelstrom of hazards that could often scarcely fail to undermine the stoutest constitution. Of recent years things have improved in this respect, and the International Labour Review[3] has described the growth of legislation designed to protect the young worker in Britain and other industrial countries; but there is still urgent need for enlightened vocational guidance. Fortunately most young people are likely to be able to do most jobs that come their way nowadays, though some at the extremes of fitness do require help. The crisis of school-leaving is never repeated, and if a young person gets into the wrong kind of work at that stage it is very difficult to get him back on to the rails again. The task of the Youth Employment Counsellor is not an easy one. He has to fit the ability and inclination of the boy to a job in which he is likely to be reasonably happy and successful; and he has to find the appropriate job quickly, for if it is not forthcoming soon there is a probability that the boy may drift into the first opening offered. Among the criteria of success that have been applied to young people in this age group are the ability to get, and to hold, skilled employment; to obtain work which satisfies the young person himself and which he is prepared to accept as his permanent job in life; and ability to conform to the

[1] *Disinherited Youth.* Carnegie Trust. 1943.
[2] *The Needs of Youth.* Oxford. 1939.
[3] *International Labour Review*, 1953, **67**, 64, 542. I.L.O., Geneva.
[4] *The Young Wage Earner.* Oxford. 1951.
[5] *Brit. J. Sociol.*, 1953, **4**, 323.

ordinarily accepted standards of social conduct and to use leisure in a reasonable and intelligent manner, Ferguson and Cunnison[4] found that, no matter which of these tests is applied, young people who come from a good home get on best.

Fortunately the teenagers enjoy comparative freedom from illness; incapacity for work is lower in this age group than at any later age, though tuberculosis is a problem among these young people. In their series of 1,315 boys who had left school at the earliest permitted age, Ferguson and Cunnison found that 54 had already, three years after leaving school, some degree of disability liable to influence their future working capacity. In a representative group of 74 18-year-old lads studied on the eve of call-up for National Service, Logan and Goldberg[5] have reported that 43 were stable and well adjusted, 19 were maladjusted in some respect, while 12 were "clearly disturbed"—"emotionally so disturbed that psychiatric help would have been advisable." This is probably a higher proportion than that found by most doctors in the student health services of our universities, though the circumstances are different; and there may be room for difference of opinion about the degree of emotional disturbance that calls for psychiatric help. The problems of youth are many-sided and compelling. To their solution medicine has a contribution to make: this is surely above all in the sphere of the family doctor.

ALCOHOL AND ROAD ACCIDENTS

The drunken driver gets short shrift from both public opinion and the law in Britain nowadays, and there seems also to be a growing awareness that the drinking of quite small quantities of alcoholic liquor can seriously impair judgment.[1 2] But the extent to which alcohol causes road accidents is unknown; indeed, it can hardly be guessed at. The police are reluctant to assign alcohol as the cause of an accident unless they have good evidence, and the evidence of whether people involved in an accident have alcohol in their tissues is not often obtained in this country. Even if it were, the question whether the amount found was sufficient to account for the accident would often be difficult to answer—impossible sometimes with any certainty. In road accidents recorded as due to drink or drugs 1,278 people in Great Britain were injured during 1952; these were 0.61% of the total road casualties. The corresponding figures for 1951 were 1,704 and 0.79, and for 1949 they were 1,269 and 0.72. These figures must seem surprisingly small in relation to the amount of travelling to and from convivial gatherings to be seen of an evening, whether by car, bicycle, or on foot—for the drunken pedestrian is also a menace. An analysis of the road accidents attributed to drink or drugs in 1951 carried out at the Road Research Laboratory of the Department of Scientific and Industrial Research[3] shows that these accidents composed 0.62% of all road accidents in England, 0.85% in Wales, and 1.98% in Scotland. Of the 1,704 casualties, 636 (37%) were pedestrians; in these 636 cases the pedestrian was to blame in 497 (78%). There were 233 bicycle casualties (14%), and in 180 (77%) of these the cyclist was the culprit. The worst period of "drink or drugs" accidents was Saturday 10 p.m. to Sunday 1 a.m., when 21% of the week's total occurred. The closing of public houses on Sundays in Wales and Scotland was found to be associated with a statistically significant lowering of the Sunday drink accident figures for these countries in comparison with those for England. Such in outline is one part of the rather shadowy background to the many telephone calls that doctors are apt to receive, just as they are dropping off to sleep, asking them to come and examine a man at the local police station. What the doctor should do when he gets there is the subject of a useful booklet published this week by the British Medical Association.[4]

In June, 1951, the Association appointed a special committee to revise and bring up to date two of its previous reports on road accidents and drunkenness, published in 1927 and 1935. The chairman of the committee was Professor E. J. Wayne, and among members were experts in many branches of medicine, including general practitioners, as well as authorities from outside the profession. After explaining the law on intoxication the committee describes in detail the examination of a person detained by the police on the suspicion of being under the influence of alcohol. The report includes guidance on such necessary preliminaries as gaining the person's consent, such questionable concomitants as the presence of a police officer, and such worrying consequences as the giving of written or verbal evidence. Most of this is procedure well tried in practice and here well expressed, a concise record of the exceptionally wide experience which the committee's members have of different aspects of the subject.

The more novel feature of the report is its discussion of estimating the alcoholic content of body fluids. In practice urine is found to be the most suitable fluid to analyse, but considerable experience of the procedure is necessary and facilities are not yet available in every district. Though no particular proportion of alcohol in urine or blood is recognized by the law of this country as signifying that the suspect was culpably drunk or not, an estimate of it can nevertheless, as the report points out, be of value for several reasons. First, a suspect may be conclusively exonerated, and the committee recommends that a suspect who protests he has taken little or no alcohol should be given the opportunity of having his word confirmed by a test of his urine. Secondly, it affords some indication of the trustworthiness of the suspect; and, thirdly, alcohol estimations may point not to a living suspect, for instance, but to a dead victim. Even so, any alcohol estimation could be

[1] Goldberg, L., *Quart. J. Stud. Alcohol*, 1950, **11**, 1.
[2] Penner, D. W., *Canad. med. Ass. J.*, 1954, **70**, 18.
[3] Jeffcoate, G. O., *Brit. J. Addict.*, 1953, **50**(1), 67.
[4] *The Recognition of Intoxication.* London: British Medical Association. 1s. See p. 753 of this week's *Journal*.
[5] See *British Medical Journal*, 1953, **1**, 1269.

misleading if the possibility was overlooked that another drug might have been taken as well. The most likely one is a barbiturate, and there is some evidence that it potentiates the effects of alcohol, though the combination if only additive would clearly be a grave risk.[5]

Confining itself to issues of more immediately practical importance, the report does not venture more than a glance at the arguments whether or not a particular level of alcohol in the blood or urine of a person in charge of a motor vehicle should be evidence that he was culpably intoxicated. In this country it is probable that the degree of intoxication below which conviction will not be obtained corresponds to a blood level of about 0.15%. In some countries figures have been agreed at which it is an offence to drive a vehicle. In Norway, for example, it is 0.05%, in Denmark 0.1%, in Sweden 0.15%, and in some states of America 0.15%. Opinion in Britain has usually veered away from making the blood level of alcohol a fixed measure of culpability, and preferred to dwell rather on the fact that people vary much in their response to different quantities of alcohol. Perhaps this has led to some neglect of the value of routine alcohol estimations (of urine) as additional evidence. If so, this report, admirable as a manual of instruction, may also serve the useful purpose of arousing interest in this debatable subject.

ANTIHAEMOPHILIC GLOBULIN

It is now believed that in the early stages of coagulation thromboplastin is formed in the blood itself as the result of a complicated interaction between a factor or factors derived from the blood platelets and several plasma factors—namely, antihaemophilic globulin, Factor V, Factor VII, and the Christmas factor.[1] In addition, contact with a water-wettable surface and the presence of ionized calcium seem to be essential. As its name suggests, one of the plasma components, antihaemophilic globulin (A.H.G.), is the substance which is absent or grossly deficient in true inherited haemophilia. The exact nature of A.H.G., which is present normally only in very small amounts in the plasma, is unknown; it mostly separates with the fibrinogen fraction (Cohn's fraction I) when plasma is fractionated by chemical methods of precipitation.

The only effective way of treating haemorrhage in haemophilia is to administer A.H.G. intravenously. This can be done by whole-blood or plasma transfusions. Large volumes are necessary—several pints of blood or plasma being required for an adult—and as A.H.G. is somewhat labile the blood or plasma should be administered within 24 hours of collection. Lyophilized fresh plasma or plasma frozen as soon as possible after collection may be used provided they are administered immediately they are reconstituted. Alternatively, the fibrinogen fraction of plasma may be administered, if available: it is this preparation that has loosely been referred to as "antihaemophilic globulin." This has the theoretical advantage of containing A.H.G. in a concentrated form. Unfortunately preparations of high and standard potency are difficult to prepare, and at present it seems best to use freshly obtained plasma, even if this means administering much larger volumes.

[1] Biggs, R., *et al.*, *J. Physiol.*, 1953, **122**, 538.

NEW FELLOWS OF ROYAL SOCIETY

Though the list of twenty-five Fellows elected to the Royal Society last week did not contain the names of any medical men, some of the distinguished scientists accorded the honour have made far-reaching contributions to the advancement of medicine. Prominent among them is Professor A. Bradford Hill, professor of medical statistics at the London School of Hygiene and Tropical Medicine. In recent years Professor Hill has been foremost among those workers engaged on the evaluation of new therapies. The large number of drugs produced in the last decade or so, often several for a single disease, such as tuberculosis, made some accurate assessment of their worth imperative. In devising the methods for doing this in conjunction with his colleagues of the Medical Research Council, Professor Hill not only put medical men and their patients in his debt but set standards of therapeutic research in Britain that have not yet been adopted on the same scale in any other country. Some years ago Professor Hill collected and analysed data for the Spens reports; more recently his name has been well-known outside medical and scientific circles for his work with Dr. R. Doll showing the link between smoking and cancer of the lung. Professor C. Rimington, who is particularly distinguished for his work on the synthesis of porphyrins, is professor of chemical pathology at U.C.H. Medical School, London. The author of many papers on blood pigments and their chemistry, Professor Rimington served the Medical Research Council as a biochemist from 1937 to 1945. Before that he had worked in the South African veterinary services for several years. Canada is honoured in the person of Professor F. C. MacIntosh, one of its foremost scientists and professor of physiology at McGill University. Professor MacIntosh formerly worked for a time at the National Institute for Medical Research, London. His researches have been concerned with the physiology of the nervous system, including the transmission of the nervous impulse. Dr. Rosalind Pitt-Rivers, who is a biochemist at the National Institute for Medical Research, has worked for some years on products of the thyroid gland, and in the last two years particularly has carried out research into thyronine. Dr. F. Sanger is a biochemist at Cambridge, a colleague there of Professor F. G. Young's. He has played a prominent part in the biochemical researches into insulin that have distinguished that laboratory, and is also an authority on the amino-acid structure of proteins. Dr. M. F. Perutz is a lecturer in biophysics at Cambridge and director of a Medical Research Council unit there for research into the molecular structure of biological systems. He is carrying out research into the structure of proteins by means of *x*-ray diffraction, and much of his work has been on haemoglobin, some of it in connexion with sickle-cell anaemia.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

THE ASSESSMENT OF ADRENAL CORTICAL ACTIVITY

BY

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In the investigation of patients with altered adrenal cortical function there are certain routine laboratory tests which may show deviations from normal and be of subsidiary value, and other specially designed tests aimed at more precise diagnosis. In this article the former will be discussed first, and then the more specific tests such as the Kepler test, the estimation of the urinary 17-ketosteroids, and the trial of A.C.T.H. Before dealing with these, however, it is convenient to review the important conditions in which changes in adrenal cortical function occur. The following is a brief classification for this purpose.

Decreased Adrenal Cortical Function

Acute.—(1) *Waterhouse–Friderichsen syndrome* (the diagnosis of this condition should be regarded as a clinical problem and it is inserted here only for completeness) and (2) *crisis in Addison's disease.*

Chronic.—(1) *Addison's disease* due to tuberculosis, "adrenal cortical atrophy," and rarely to invasion by tumour, amyloid disease, etc. (2) *Anterior hypopituitarism* may be due to post-partum necrosis (Simmonds's disease), chromophobe adenoma, cranio-pharyngioma, and other rarer lesions. In these patients partial atrophy of the adrenal cortex occurs owing to lack of adrenocorticotrophin secretion by the pituitary. (3) In rare cases children with *adrenal virilism* may have accompanying Addison's disease owing to lack of secretion of cortisone and hydrocortisone by the glands.

Increased Adrenal Cortical Function

Adrenal Virilism.—Pre- or post-pubertal, due to "hyperplasia" or tumour of the adrenal cortex.

Male Feminization.—Rare cases associated with adrenal cortical tumours.

Cushing's Syndrome.—A small proportion of these cases may be due to primary tumour of the adrenal cortex.

Laboratory Investigations of Subsidiary Value

Blood Counts

In increased adrenal cortical activity of the type seen in Cushing's syndrome a characteristic blood picture is often encountered. Haemoglobin and red-cell counts are usually raised, a haemoglobin level of 110% Haldane, even in women, being expected. The total white-cell count is not demonstrably abnormal, but there is a definite tendency for the polymorphs to rise and the lymphocytes to fall, changes which are best evidenced in the fall in lymphocytes to levels below 25%. The direct eosinophil count may be of value in showing a reduction in the number of these cells to the lower limits of normal or below. (Their usual range is between 25 and 300 cells per c.mm.) For this determination the blood should be collected freshly by the pathologist.

Although all these changes tend to be reversed in Addison's disease and hypopituitarism the values seldom deviate very significantly from normal levels. A few patients with hypopituitarism are found to have a mild macrocytic type of anaemia.

Carbohydrate Metabolism

A proportion of patients with Addison's disease show a tendency to hypoglycaemia on fasting. This may be apparent after the lapse of 24 hours and is gradually progressive with a longer duration of fast. If this tendency is present these patients respond unfavourably to fasts of this duration and may drift into a crisis. Blood-sugar levels below 50 mg. per 100 ml. may occasionally be reached with the development of hypoglycaemic crisis. Patients with hypopituitarism also possess this tendency in a variable degree. Both these groups of patients respond profoundly to the injection of small doses of insulin; for example, a dose of 4 units of soluble insulin may be a large one to the rare patient developing severe diabetes in the presence of Addison's disease. This emphasizes that the standard insulin-tolerance test based upon the injection of 0.1 unit per kg. body weight intravenously is apt to be dangerous, promoting a profound fall of blood sugar which the patient is unable to overcome. Such investigations should never be carried out outside hospital, and substandard doses of insulin must be employed. The administration of oral glucose to these patients results nearly always in a "flat" type of tolerance curve where only low levels of blood sugar are reached after half an hour and one hour. Thus in extreme cases the blood-sugar level may never rise above 100 mg. per 100 ml.

Patients with Cushing's syndrome often show decreased tolerance to carbohydrate; glycosuria, fasting hyperglycaemia (blood sugar greater than 120 mg. per 100 ml.), and a diabetic type of oral glucose curve may all be apparent.

Basal Metabolic Rate

A decrease in the basal metabolism, as would be expected from the secondary hypothyroidism, is nearly always found in patients with hypopituitarism, and values down to minus 40% found in myxoedema are encountered. In Addison's disease there is a tendency to a secondary decrease in the basal metabolism, the average lying within the lower limit of the normal range of minus 15%.

Changes in Blood Chemistry

In Addison's disease characteristic changes in the serum electrolytes are found in the more advanced stages of the disease. The constant renal leak of sodium from decreased tubular reabsorption of this ion results, especially if the intake is insufficiently high, in a decrease of extracellular fluid volume and of its total sodium content. Continued shrinkage of this fluid entails depletion of the volume of blood plasma and the concentration of sodium in both these fluids. This process is accompanied by a rise in the packed cell volume (haematocrit) if the patient is not too anaemic to mask it. This rise in packed cell volume is likely to indicate an impending crisis and can be of value in following the efficacy of intravenous replacement therapy. The low values for serum sodium (below 135 mEq per litre or 310 mg. per 100 ml.) are accompanied by a similar drop in the serum chloride below 95 mEq per litre (560 mg. per 100 ml. expressed as NaCl, or 365 mg. per 100 ml. expressed as Cl). A further finding which may be of corroborative assistance is a rise in the level of serum potassium above 5.5 mEq per litre (or 22 mg. per 100 ml.). In performing estimations for this ion it is essential that the serum be separated from the blood within an hour and that no haemolysis should be present, since the red cells contain very much greater concentrations of potassium than the plasma. In Addisonian crisis these changes tend to be at a maximum and the carbon dioxide combining power of the

plasma rises slightly. The accompanying dehydration results in a moderate rise in the blood urea and non-protein nitrogen values.

In hypopituitarism there is also a tendency to lowering of the serum sodium and chloride levels, but this is not so marked as in Addison's disease, so that the changes are not easily apparent and the investigation is not worth while. In Cushing's syndrome a curious imbalance is encountered, so-called hypochloraemic alkalosis. The chloride level falls and the carbon dioxide rises to a small degree. There is an accompanying tendency for the potassium level to fall below 3.5 mEq per litre (14 mg. per 100 ml.). These alterations are of very subsidiary value in the diagnosis of the syndrome.

The Water Test (Kepler Test)

In patients with appreciable decrease of adrenal cortical activity due either to Addison's disease or to hypopituitarism it is found that the excretion of urine follows a more uniform pattern through the day than in normal persons. As a consequence of this the decreased ability to economize in urine volume during the night and to show a diuresis during the day is made use of in the investigation proposed by Robinson, Power, and Kepler at the Mayo Clinic (Kepler test). This test is relatively simple to perform and is one of the most valuable screening tests in the diagnosis of these syndromes. It may be of great value in suggesting the possibility of adrenal cortical insufficiency in the absence of pigmentation. It should never be applied to patients suffering from renal disease or oedema due to any cause.

The test is divided for convenience into two parts. For its performance the patient should be in bed, but admission to hospital is not necessary if adequate facilities can be arranged to make and measure accurately the necessary urine collections over timed periods. The co-operation of the patient in complete emptying of the bladder at the end of each period is also necessary. The first part is carried out by withholding all fluids and food after 6 p.m. After emptying the bladder at 10.30 p.m. urine is collected from 10.30 p.m. until 7.30 a.m. the next morning. The patient is then given 20 ml. of water per kg. body weight (9 ml. per lb.) to drink during 45 minutes. Urine collections are made at 8.30, 9.30, 10.30, and 11.30 a.m. and at 12.30 p.m. If the largest volume of urine excreted during a single hour between 8.30 a.m. and 12.30 p.m. ("day urine") exceeds the volume of the 10.30 p.m. to 7.30 a.m. specimen ("night urine") the result is negative for adrenal cortical insufficiency. If the reverse is true the test is positive. Several shortened and more convenient versions of this test have recently been proposed, but their use is not advised for the data for their interpretation are at present lacking.

The accuracy and specificity of the test are greatly enhanced if the second part is also carried out. This involves obtaining, before the water is administered to the patient, a specimen of oxalated blood for chloride and urea determinations. A specimen of the "night urine" with a note of its volume and the volume of "day urine" should also be sent to the pathologist. The test depends upon the fact that the clearance of chloride is increased in cortical insufficiency and the clearance of urea tends to be decreased. These variables (expressed in mg. per 100 ml.) are multiplied to the urine volume observations thus:

$$\text{Factor} = \frac{\text{Night urine urea}}{\text{Blood urea}} \times \frac{\text{Plasma chloride}}{\text{Night urine chloride}} \times \frac{\text{Volume of day urine}}{\text{Volume of night urine}}$$

Adrenal cortical insufficiency may be regarded as present if the factor is less than 25.

The results of both parts of the test can be interpreted only in an all or none fashion, as they give no information about intermediate degrees of failure. If the second part is applied many less false-positive results are obtained and the number of false negatives diminished. The two parts together, when used for the first time, are positive in about 80% of cases of Addison's disease, but occasional false positives are also obtained in patients with liver disorders, hyperthyroidism, anorexia nervosa, gastric lesions, and sprue, so that the results can be interpreted only in the light of other known factors. The test, however, has the advantage that treatment of the patient with deoxycortone does not alter an abnormal test for adrenal cortical insufficiency into a negative one. Treatment with cortisone can of course effect this change.

Urinary 17-Ketosteroid Determinations

There are excreted in the urine a large number of metabolites of adrenal cortical hormones. The determination of one group of these, the 17-ketosteroids, in which a ketone grouping (=C=O) is present at the seventeenth carbon position in the steroid "nucleus" in ring D, may be considered to be a basically reliable procedure. Substances of the same type and giving the same chemical reaction are excreted as the end-products of the metabolism of testosterone, itself secreted by the interstitial cells of the testes. There is no significant corresponding source of 17-ketosteroid in women, so that this must be taken into account in interpreting the results. A further factor is the variation of technique employed in different laboratories. It is to be hoped that this difficulty may be mitigated by the publication of a recommended technique from the Committee on Clinical Endocrinology of the Medical Research Council.* In my laboratory, which may be taken as a guide, the normal range for adults between the ages of 20 and 40 is taken as 8–23 (average 14.5) mg. a day for men, and 5–18 (average 9.5) mg. a day for women. In older individuals these values fall away by 50% at the age of 70. In children of both sexes up to the age of 8 the excretion is up to approximately 1 mg. a day; up to the age of 12 it rises to 4 mg. a day, and then after puberty is established adult values are reached. Day-to-day variations of up to approximately one-third may be encountered in a given person.

Careful 24-hour collections of urine are required. The patient is instructed to empty his or her bladder at the start of the collection and discard the urine. All the urine excreted during the subsequent 24 hours, including the specimen passed at the conclusion of the period, is collected. The urine is preferably acidified (by adding 10 ml. of dilute hydrochloric acid *B.P.* to the collection). A note of the total volume and a sample of about 200 ml. should be sent to the pathologist undertaking the estimation.

The determination of 17-ketosteroids may be of ancillary value in the diagnosis of Addison's disease. Values are usually less than 7 mg. a day, with a definite tendency for lower values in women than in men, as would be expected. In the presence of normal values the diagnosis is likely to be wrong. In interpreting reductions of this order it must be remembered that any chronic illness may lead to similar changes. It is advisable not to have the patient on cortisone therapy, but again deoxycortone does not interfere. In hypopituitarism values are often lower and approach zero in both sexes, so that the diagnostic value is greatly increased. This is partly owing to the fact that in the male the testicular component is also reduced in this condition. Patients with anorexia nervosa, the differentiation of which from hypopituitarism may be difficult, sometimes have normal values or they may be decreased to Addisonian levels as a result of the inanition.

Increased adrenal cortical activity due to hyperplasia and producing adreno-genital or virilizing syndromes always results in a rise in 17-ketosteroid excretion. This is most pronounced in adults who have developed virilism before puberty, in whom values up to approximately 100 mg. a day may be reached. The post-pubertal variety of this syndrome in girls has to be differentiated from "idiopathic hirsutism" and may show only quite moderate rises in excretion to about 40 mg. a day. In some of these patients with a similar clinical picture the underlying lesion may be

Lancet, 1951, 2, 585.

an adrenal cortical tumour, an uncommon lesion. In about half the cases this is accompanied by the excretion of large amounts of 17-ketosteroid, and many biochemists feel that a level in excess of 100 mg. a day is likely to be indicative of tumour. It is possible by applying colour reactions for dehydroepiandrosterone and its relatives to obtain some further assistance. A proportion of tumour cases show an increase in the excretion of this steroid. Unfortunately the cases in which there is most difficulty, those with lower levels of 17-ketosteroid excretion, are the least likely to show a rise in dehydroepiandrosterone.

In Cushing's syndrome the help obtained from 17-ketosteroid excretion is much less. This clinical picture may also be due to increased adrenal cortical activity or to a tumour. In the former case a minority of patients show a small elevation of 17-ketosteroids to about 30 mg. a day. The findings in the tumour cases are similar to those discussed for tumours causing the virilizing syndromes. It is inadvisable to have any of the patients in these groups receiving cortisone when 17-ketosteroids are determined. When interpreting a rise in 17-ketosteroid excretion it should be remembered that the rare interstitial tumour of the testes causes a large increase for the age of the patient and a rise may also result from arrhenoblastoma in women.

Trial of A.C.T.H.

The attempt to stimulate the activity of the adrenal cortex by the use of A.C.T.H. and measure the response obtained may be of the greatest value in the diagnosis of Addison's disease and helpful in cases of anterior hypopituitarism. In advanced Addison's disease it seems that destruction of the adrenal cortex is complete. In less severe cases and cases of hypopituitarism destruction is not complete, so that some degree of stimulation of the cortex is possible. There are two ways of using A.C.T.H. that may be helpful.

Eosinophil Test.—At about 10 a.m. an eosinophil count is made in the peripheral blood and 25 international units of lyophilized A.C.T.H. injected intramuscularly. After four hours the count is repeated. Normal individuals show a pronounced fall in the eosinophils under these conditions. If the test shows a decrease of less than 50% in the count the patient is likely to have Addison's disease or severe hypopituitarism. Repetition of the test makes the diagnosis much more certain. Patients with a small degree of cortical destruction or atrophy may give a normal response. The validity of the test is interfered with in some patients with eosinophilia, and tests in which the initial eosinophil count is very low (below 50 cells per c.mm.) should be disregarded.

Excretion of 17-Ketosteroids.—The most stringent diagnostic test for complete adrenal cortical insufficiency is to measure the change in 17-ketosteroid excretion after adequate adrenal cortical stimulation. Several methods have been proposed for the procedure, but one of the best seems to be as follows. The 17-ketosteroid excretion is measured in two consecutive 24-hour periods and the patient is then given 20 units of A.C.T.H. gel intramuscularly 12-hourly for 48 hours. The 17-ketosteroid excretion is measured again for the last 24 hours of the period. A significant increase (exceeding 50% of the baseline level) indicates that the adrenal cortex is responsive. This test is elaborate and will probably have to be carried out in hospital. Both these tests are at present subject to the restricted supplies of A.C.T.H. available.

Conclusions

It will be appreciated that the use and interpretation of laboratory tests in these conditions require careful judgment. In order to draw the correct inferences all the facts, especially the clinical findings, must be given their due weight. For instance in this article the discussion has been limited to the question of deciding whether adrenal cortical function shows serious deviations from normal. Decreased function results from either a primary lesion of the gland or secondary atrophy due to diminished pituitary function. In the latter event evidence of decreased function of other endocrine glands, particularly the gonads, should be forthcoming. Rarely the differentiation of the two conditions may be a difficult matter. Some of the procedures described would be better carried out in hospital. They are considered here partly to remind the reader of their interpretation, which may be of value when hospital reports on patients are received.

It will be appreciated that most of the tests considered afford only indirect evidence of the behaviour of the adrenal cortex and that other factors may intervene between the secretion of this gland and the final manifestation measured in the test. For this reason measurements of steroids, perhaps in blood, may be the most valuable test in the future. It is evident that 17-ketosteroid determinations have their limitations. It is hoped that other measurements of adrenal cortical steroids and of other metabolites may be more definitive. Several techniques have been proposed for this —for example, determinations of "11-oxysteroids" and "reducing steroids"—but at present no method has been developed which may be regarded as satisfactory for routine use and which can be recommended in this article.

Next article on Clinical Pathology.—"Serological Tests in Diagnosis," by Professor E. T. C. Spooner.

RECOGNITION OF INTOXICATION

With the publication this week of a report on "The Recognition of Intoxication," the B.M.A.'s Committee on Alcohol and Road Accidents* has completed the first half of its work. Appointed in June, 1951, the Committee was instructed to revise and bring up to date the Association's Reports on Tests for Drunkenness (1927) and The Relation of Alcohol to Road Accidents (1935). The Committee is awaiting results of experimental work now in progress on the physiological effects of alcoholic intoxication before revising the report on road accidents.

"The Recognition of Intoxication" is intended as a guide for those who are called upon to examine persons detained by the police on the suspicion of being under the influence of alcohol. The examiner is often a general practitioner, and the report is written primarily to help general practitioners in the discharge of this difficult and anxious task.

The Medical Examination

First comes a brief explanation of the Law relating to alcoholic intoxication. The Road Traffic Act, 1930, makes it not simply a question of deciding whether a person is drunk in the popular sense, but whether he "is under the influence of drink or a drug to such an extent as to be incapable of having proper control of the vehicle." Then follow two important sections on the medical examination itself. The first deals with points of procedure, such as obtaining consent and the degree of privacy that may reasonably be expected. One of the main purposes of the examination is to exclude other causes of unusual behaviour, and if such are present to decide how far they influence the clinical picture. A fairly comprehensive list of these is given, with some tips to help in differential diagnosis. There is advice on taking specimens for the estimation of alcohol content, and on making a second examination at a later date. Finally there is a word about what information should be given to the detained person and to the police. The second section consists in a "model scheme" of medical examination. Making the examinee walk along a straight line is condemned. The examiner is warned to base his opinion on the results of the whole examination, and not to draw conclusions from isolated features.

*Professor E. J. Wayne (chairman), Dr. Robert Forbes, Dr. E. A. Gregg, Dr. F. E. Camps, Dr. E. A. Carmichael, Dr. Macdonald Critchley, Dr. A. B. Davies, Colonel A. H. Farley, Dr. T. C. N. Gibbens, Dr J. A. Gorsky, Professor A. St. G. Huggett, Dr. J. C. Matthews, Dr. T W. Morgan, Mr. F. R. J. Peel, and Professor R. J. V. Pulvertaft.

Evidence in Court

After dealing with the form in which a doctor called by the police should record his opinion, the report goes on to consider the evidence which may have to be given in court. "Whether called for the prosecution or the defence (the doctor) should present, without bias, the medical opinion he has formed . . . and, with his scientific knowledge, help the court to arrive at the facts of the case." He should take care not to act as a partisan witness nor to be drawn into legal arguments. It is for the court alone to decide whether the accused person has committed an offence.

Estimation of Alcohol in Body Fluids

Among the data which may help the doctor to estimate the degree of intoxication is the concentration of alcohol in the body fluids. The report recommends the use of urine for this purpose. Urine samples are easier to collect than blood if the subject is obstreperous, and the results equally useful. An estimate of the urine alcohol level may help the court in one or more of four ways: it may conclusively exonerate the person charged; it can serve as a useful check on his veracity, as the alcohol content of the tissues is generally accepted as an accurate indication of the minimum quantity consumed; it may show that it was the victim of an accident who was intoxicated rather than the driver; and, lastly, it may be used—with circumspection—as indirect evidence of incapacity to control a vehicle. The report discusses some of the evidence linking blood alcohol levels with performance, but it is careful to stress that the responses of different individuals to the same concentration of alcohol vary widely. The Committee is continuing its consideration of this problem and will deal with it more fully in its second report.

TABLE I

Minimum Intake of Ordinary Beer or Stout as Calculated from the Alcohol Content of the Urine

(For a male of body weight of 11 st. (70 kg.) and assuming beer and stout to contain 14.7 g. alcohol per pint.)

Urine Result in mg./100 ml.	Intake in Pints	Urine Result in mg./100 ml.	Intake in Pints
24	½	367	7½
49	1	391	8
73	1½	416	8½
97	2	439	9
123	2½	464	9½
147	3	488	10
171	3½	513	10½
196	4	537	11
220	4½	561	11½
244	5	587	12
268	5½	611	12½
293	6	635	13
317	6½	660	13½
343	7	684	14

TABLE II

Minimum Whisky or Gin Intake as Calculated from the Alcohol Content of the Urine

(For a male of body weight of 11 st. (70 kg.) and assuming whisky and gin to contain 8.98 g. per fluid ounce.)

Urine Result in mg./100 ml.	Whisky* in fl. oz.	Urine Result in mg./100 ml.	Whisky* in fl. oz.
30	1	420	14
60	2	450	15
90	3	480	16
120	4	510	17
150	5	540	18
180	6	570	19
210	7	600	20
240	8	630	21
270	9	660	22
300	10	690	23
330	11	720	24
360	12	750	25
390	13	780	26
400	13⅓ (=⅓ bottle)	800	26⅔ (=1 bottle)

* 1 whisky = ⅔ fl. oz. approx. 1 double whisky = 1⅓ fl. oz. approx.
Note.—1 pint = 0·6 litre : 1 fl. oz. = 28 ml.

The last section of the manual is based on the report† of a panel of the Royal Institute of Chemistry, which the Council of the Institute appointed to help the Committee. It deals with the technical aspects of determining the blood and urine alcohol concentrations. Detailed instructions are given on how to collect specimens, and the chemical analyses are described in two appendices. This section also discusses the translation of the results of these laboratory investigations into terms of pints of beer or ounces of spirits consumed. Two conversion tables are given (Tables I and II) relating the urine alcohol level to intake for an 11-stone man. These tables show the *minimum* amount of alcohol in the body; in the average case the amount would undoubtedly be rather higher—it certainly could not be lower. For this reason the Tables cannot be used to estimate the probable urine or blood alcohol content from a knowledge of the amount of alcohol taken.

Factors for differences in body weight and sex are provided. For women the answer in pints of beer or ounces of spirits must be multiplied by 3/5. If blood alcohol figures are used instead of urine alcohol figures the result must be multiplied by 4/3.

The report ends with a list of offences in which "drunkenness" plays a part. These are the offences, in addition to those under the Road Traffic Act, in respect of which a doctor might be asked to express an opinion on the sobriety of the defendant or other persons. They range from being "drunk in any street and guilty of any riotous or indecent behaviour therein" to being a drunken person who refuses or fails to quit licensed premises "upon being requested to do so."

The report may be obtained from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1. It is free to members of the medical profession; to others it costs 1s. (including postage).

PAUL EHRLICH AND EMIL VON BEHRING

CENTENARY CELEBRATIONS

Over 600 men and women from different parts of the world gathered together in Frankfurt am Main a fortnight ago to do homage to the memory of Ehrlich and von Behring, the subject of commemorative articles in last week's *Journal*. The hosts were the Paul Ehrlich Institute, the Philipps University of Marburg a. d. Lahn, and the Johann Wolfgang Goethe University of Frankfurt. Generous hospitality was provided by the Farbwerke Höchst A.G. The opening ceremony in the Paulskirche (no longer a church) began and ended with music and was presided over by Dr. Theodor Heuss, the President of West Germany, who in his address recalled his meeting many years ago with Einstein, whose birthday fell on the same day as Ehrlich's. Two of Ehrlich's daughters and two grandsons were present, as well as descendants of von Behring. The solemnity of the proceedings was heightened by the magnificent robes of the Rectors of Frankfurt and Marburg Universities—Professor O. Gans and Professor W. Walcher, and somewhat marred by the ubiquitous photographer and the glaring lights of the cinematographer. In fact when Professor Gans bestowed the Ehrlich Prize on Professor E. B. Chain a horde of camera-men prevented the audience from witnessing the principal event of the morning. After a word of greeting from Professor R. Prigge, director of the Paul Ehrlich Institute, speeches were made by the Minister of Education of Hesse and the Minister for Internal Affairs of West Germany.

The Ehrlich Prize Oration

Professor Chain, in acknowledging the prize, made handsome acknowledgment to the numerous workers who had played a part in the discovery of penicillin. After a tribute to Ehrlich's work and to the discovery of prontosil in 1935 by Domagk, the orator said that a new era began when,

†Kent-Jones, D. D., and Taylor, G., *Analyst*, 1954, **79**, 121.

in 1940, Florey, himself, and their co-workers isolated penicillin at Oxford as a metabolic product of *Penicillium notatum*. But before the turn of the century Pasteur and others had observed the antibacterial action of substances obtained from bacteria and moulds. Fleming's discovery in 1929 of what he then named penicillin, and of the inhibiting effect of a filtrate on the growth of staphylococci, passed for the time being unnoticed. Fleming suggested that his culture extract could be applied in the local treatment of infected wounds, but the instability of penicillin made its use impracticable. Three years after Fleming's discovery Raistrick tried, without success, to isolate the active principle from filtrates of *Penicillium notatum*. Professor Chain emphasized that Florey and he began their work a year before the outbreak of war from a purely biochemical angle, and did not expect to find a preparation which could be applied clinically. To-day one could state that penicillin was the most active and least toxic of chemotherapeutic remedies. The only side-effect was an allergic reaction in about 5% of treated cases. Staphylococci did not develop resistance against penicillin. Staphylococci not affected by penicillin were those which produced penicillinase. Penicillin killed off bacteria only when they were actively growing, thus differing from most other antibacterial substances. After a review of other antibiotics, Professor Chain suggested that the expression "broad spectrum" was not altogether happy—the wider the spectrum of an antibacterial substance the less was its specificity and the greater its toxicity. In other words a "broad spectrum" implied a general protoplasmic poison. He concluded by saying that the search for new antibiotics must go on, especially for the treatment of tuberculosis and virus infections. Further progress would be achieved only through the aid of chemical microbiology as a department of biochemistry.

Ceremony at Marburg

Marburg, an old university town, provided a charming contrast to bustling, largely rebuilt Frankfurt. The university, dating from 1527, was the first protestant university to be founded. After the procession of university authorities entered the Hall to the music of Handel, the Rector, Professor W. Walcher, gave an address and bestowed the von Behring prizes for 1948, 1952, and 1954 on Professor H. Schmidt, Sir Macfarlane Burnet, and Professor M. Heidelberger respectively.

Allergy and Immunity

In a lecture on the relations of allergy to immunity Professor Schmidt recalled the first fatal case in 1896 resulting from the prophylactic injection of an antitoxic serum. It was logical to assume that infection would be followed by allergy to the infecting micro-organism and its antigens. Two main questions posed themselves: (1) How far were the characteristic symptoms of an infectious disease due to allergy? (2) What was the relation between allergy and immunity? The body became allergic to tubercle bacilli if a focus of infection containing living bacilli existed in it, and what was known as Koch's phenomenon prevented superinfection from becoming a progressive disease. On this basis von Behring tried to protect cattle against tuberculosis with a vaccine prepared from human tubercle bacilli. In principle, Professor Schmidt claimed, von Behring's method corresponded to that of Calmette in the prophylactic use of B.C.G. in man. Was the protection afforded by B.C.G. vaccination due to the concomitant allergy? Experiments with guinea-pigs made tuberculin-positive when immunized with sheep blood cells adsorbed with tuberculin showed that the course of tuberculous infection in them was the same as in normal guinea-pigs. But this did not prove that immunity and allergy were independent of each other, for tuberculin was but a partial antigen. If it were possible to immunize non-infected man with the complete antigens of the tubercle bacillus, the immunity could not last so long as that provided by B.C.G., but, with repeated injections, could be made more effective. Passive immunization with sera of healthy individuals previously hyperimmunized might be of therapeutic value. "And here," concluded Professor Schmidt, "I am falling into line with von Behring's aim of preparing an antitoxic serum in the treatment of tuberculosis."

Viruses, Enzymes, and Genetics

Sir Macfarlane Burnet briefly described the work on viruses in progress in the Walter and Eliza Hall Institute in Melbourne. During the recent war work was concentrated on means of immunizing against influenza, "with the ever-present fear that the experience of 1918–19 might be repeated." The methods of handling influenza virus in chick embryos were worked out, largely in his laboratory. Then Hirst in New York discovered the haemagglutinating activity of the virus. The war over, they decided to make a systematic attack on the problems presented by haemagglutination. Until 1941 they had understood that viruses acted only on susceptible cells and that their existence could be recognized only by the lesions or symptoms produced as a result of intracellular multiplication in susceptible tissues. Hirst showed that the haemagglutination was a function of the virus particles themselves, the particles adhering firmly to the cell surface. A single virus particle attached to two cells acted as a bridge holding them in contact and helping to build up the visible clumps seen in an agglutinated suspension. Another basic feature of the reaction shown by Hirst was that after a time the virus elutes off the cells, leaving them inagglutinable by ffesh virus, the eluted virus, however, retaining the power to agglutinate fresh cells. Hirst was clear that the virus acted as an enzyme, and the first phase of the work at Melbourne was to seek the nature of the virus enzyme. After seven years' work, Sir Macfarlane continued, he could now say that during the past year his colleague Dr. Gottschalk had shown that the virus acted as an amidase, breaking the CO–NH_2 link between 2-carboxy-pyrrole and hexosamine, both of which are present as part of 200 or more prosthetic groups on each macromolecule of certain mucoproteins. Chemical, physical, and biological techniques enabled them to build up a picture of the cell surface—in the first instance of the erythrocyte in its relation to the viruses that attached to it. Over the surface of the virus particle there were many enzymically active groupings, each of which could unite with and, in appropriate conditions, destroy the substrate receptors scattered over the length of the mucoprotein macromolecules. As soon as a virus particle collided with the cell surface many bonds were formed which together held the particle firmly on the cell. But as each pair of reactants developed an appropriate mutual orientation the corresponding bond was broken by enzymic action and a new bond could be then formed elsewhere. "We can almost picture the virus particle browsing like a sheep over the receptors of the cell surface until the concentration of the substrate group becomes too low to hold the virus and the cell in physical contact."

One of the implications of the enzymic attack pictured by Gottschalk was that with each splitting of a receptor an amino group was exposed and a positive electric charge added to the cell—which in practice meant a diminution of its net negative charge.

The surface reactions described were equally important in relation to cells susceptible to attack by the influenza virus. It could be shown that the influenza virus was adsorbed to the cells lining the allantoic cavity of the chick embryo or the respiratory epithelium of the mouse lung, and that the adsorption was to the same type of receptors as were present on the red cell.

As an accidental result of experiments in 1949 they had, Sir Macfarlane said, since then concentrated on the study of virus genetics. First they were concerned to see what happened when a neurotropic influenza virus was inoculated in the mouse brain with a non-neurotropic virus of different serological type. If the amount of the latter was much larger than that of the former no illness resulted —a typical interference phenomenon. But at the level where delayed illness resulted it was often possible to isolate from

the brains of the mice a new type, stable on subculture, in which the serology of the non-neurotrope was combined with the capacity of the other parent strain to produce encephalitis. Their transference of neuro-pathogenicity from one serological type of virus to another was probably the most striking example of recombination in influenza viruses. All recombination experiments in influenza were based on the hypothesis that genetic interaction occurred only when particles of each type entered the cell simultaneously. Among the conclusions of the work outlined by Sir Macfarlane was that possibly all forms of virulence were associated with a special type of recombination, suggesting that virulence developed by the accumulation of multiple genetic units. He concluded by emphasizing the value to general biological workers of such specialized studies of the influenza virus. In some ways the interaction of a virus with the cell it infected provided a potentially illuminating approach to the fundamental processes in the cell. The invading virus was a probe they could learn to use in the study of the most basic of all biological problems—the replication of organic pattern.

Antibodies

In a lecture on the formation, measurement, and persistence of antibodies in man, Professor M. Heidelberger, of Columbia University, said that the two main theories of the formation of antibodies rested upon little direct experimental evidence. According to the theory of Breinl and others antigen present at the site of globulin formation disturbed the normal synthesis in such a way that the globulin newly formed was able to react with antigen subsequently encountered. Burnet's theory was that antigen need be present only long enough to change in a specific way the enzymes or framework on which the globulin was constructed. Burnet's conception was that the enzymes were "trained" by the initial injection, and this would explain the rapid and extensive production of antibodies on reinjection of the antigen. Methods devised by F. E. Kendall and himself for estimating antibodies in the sera of hyperimmunized animals enabled them to foresee a method for the isolation of pure antibody and to furnish the last link of evidence in the chain showing that antibodies actually were serum globulins. (For the discovery of type-specific bacterial polysaccharides Professor Heidelberger and Dr. O. T. Avery received the Ehrlich prize in 1933.) There was a difference in the response to pneumococcal polysaccharides and to diphtheria toxoid. The antibodies to the former rose to a maximum in two to six weeks and stayed at that level for months, and so long as antibody persisted there was no response to reinjection of the same polysaccharides. After injection of diphtheria toxoid there was a quick rise of antitoxin and initial rapid decline, with a secondary response on reinjection of toxoid. Neither of the two theories of antibody formation provided a wholly satisfactory explanation of the known facts.

SCIENTIFIC SESSION

The final day of the celebrations was devoted to a scientific session in the premises of the firm Farbwerke Höchst A.G., at Höchst, just outside Frankfurt. Professor T. Madsen, of Copenhagen, presided during the morning and Sir Henry Dale during the afternoon. Space permits only a brief summary of the proceedings.

Mode of Action of Penicillin

Dr. E. F. Gale, Cambridge, said that "the discovery of penicillin by Fleming in 1929 heralded not only a revolution in medicine but also a new approach to the study of synthetic mechanisms in living cells." Penicillin became, and still remained, the supreme example of Ehrlich's "magic bullet." Penicillin killed cells in the process of growth, but had no demonstrable effect on the metabolism or viability of non-growing cells. Penicillin had no effect on the respiration or fermentation of washed suspensions of staphylococci. But, if penicillin was added to the medium during growth, respiration remained normal for a time, and then progressively decreased, and, with this, viability. Work at Cambridge showed that *Staph. aureus* growing in an amino-acid-rich medium accumulated high concentration of glutamic acid during growth, the concentration increasing with growth. Penicillin interfered with this concentration of glutamic acid before any effect was noticed on respiration or fermentation. Dr. Gale summarized the action of penicillin on a growing culture of *Staph. aureus* thus: (1) immediate disturbance of the synthesis of ribonucleic acid and of glycerophosphoprotein complex, (2) increasing accumulation of extractable nucleotides, (3) progressive loss of ability to accumulate glutamic acid and to oxidize guanosine, and (3), after some hours, failure of the oxidative mechanisms. Reviewing work on the effects of penicillin on suspensions of washed *Staph. aureus* cells, Dr. Gale said it appeared that penicillin reacted with the protein in such a way as to prevent it combining with nucleic acid. The synthesis of protein and of ribonucleic acid seemed to be closely associated in the growing cell. The synthesis of ribonucleic acid was partially inhibited in cells growing in the presence of penicillin. It would seem, he concluded, that they were on the verge of an explanation of the mode of action of penicillin, an explanation that involved an understanding of protein synthesis. Their probings into the action of the one would assist the elucidation of the other.

Trichomycin

Professor Seigo Hosoya, of the Institute for Infectious Diseases, Tokio, briefly described results obtained by "trichomycin," an antibiotic isolated from a streptomyces. It was active *in vivo* and *in vitro* against protozoa, such as *Trichomonas vaginalis, Treponema pallidum, Entamoeba histolytica* and against several kinds of moulds. It prevented the growth of *Trichophyton* and *Candida*, and was therefore the only antibiotic clinically effective against mycotic infections. Its significance was principally in gynaecology and dermatology. A growth-inhibiting effect could be demonstrated on the cancer cells of "Ehrlich's ascites tumour of mice."

Virus Chemotherapy

Dr. Gustav J. Martin, of the National Drug Company, Philadelphia, said that a discussion of this subject must centre on a consideration of the fundamental biochemical properties of the viruses themselves and of the basic virus-host interrelationships. The response of viruses to chemotherapeutic agents seemed to be a function of size. The largest organisms, such as members of the psittacosis-lymphogranuloma group, responded to sulphonamides and antibiotics. At the other end of the scale some of the neurotropic agents responded to no known agents. Dr. Martin then went on to discuss the inhibition of virus growth by amino-acids and their analogues, by purines and pyrimidines, by vitamin analogues, by antibiotics, and by specific enzyme inhibitors. He concluded that specific virus chemotherapy did not exist, and that "as the patterns of metabolism of the viruses emerge specific chemotherapeutic agents will become available as a matter of course."

Treponemal and Trypanosomal Infections

Dr. R. Fussgänger, of the Farbwerke Höchst, said that, as his firm was originally occupied with the large-scale manufacture of salvarsan only, systematic research on the organic compounds of arsenic did not begin until 1922. Of the 5,000 arsenicals synthesized in their laboratories only a few were released for sale. The problem of drug-resistance had strongly influenced the direction of their research. It first became apparent in connexion with tryparsamide in the treatment of trypanosomiasis. Experiments with strains resistant to various arsenicals had resulted in a new compound, "spirotrypan," which was stable, possessed a relatively low toxicity, and was active against arsenic-resistant strains of trypanosomes. Dr. Fussgänger then referred to work on the quinaldines, which in England had led to

the development of "antrycide." A diquinaldine-urea compound, "surfen," was actively bactericidal and, combined with penicillin, was effective against penicillin-resistant staphylococci. Further developments of this work had led to the production of a compound low in toxicity and non-irritant to tissues—named "babesin" because of its action against *Babesia canis*. It was active against numerous kinds of trypanosomes. Dr. Fussgänger's observations on the treatment of syphilis by "melusin"—a diazoamino compound containing no arsenic or other metals—were elaborated by Dr. J. Kimmig, of Hamburg. It was stable in dry form, but the watery solution decomposed easily. Given intravenously it brought about rapid healing of the primary syphilitic lesion. Further extensive clinical trials were necessary.

Virus Vaccines

In the afternoon, with Sir Henry Dale presiding, Dr. Herald R. Cox, of the Lederle Laboratories, Pearl River, New York, read a paper on the prophylaxis of viral diseases by the use of living vaccines. Jenner's use of cowpox or vaccinia virus on a large scale to protect against smallpox was, he said, the first instance of immunization by a living attenuated virus. Pasteur's discovery of preventive inoculation with attenuated living bacteria was an accidental discovery. Virulent cultures of chicken cholera organisms left in the laboratory during a holiday became avirulent, but were found to act as preventive vaccines when inoculated birds were later injected with virulent material. Later he established the important principle that the invasive and pathogenic properties of a virus could be altered by successive passages through appropriate hosts. These basic investigations of Jenner and Pasteur had been extended until to-day at least thirteen different viral agents were being used as living attenuated vaccines in human and veterinary medicine. The greatest success in immunizing against viral infections had been achieved by the use of living mutants lacking the invasiveness and pathogenicity of the parent strain but retaining the same antigenic structure.

Certain specifications must be met before a reliable vaccine could be safely used. (1) It must be safe, and not induce a severe or fatal infection in the immunized host. (2) It must be so attenuated that it would not only be innocuous in the host, but have such low virulence that it could not be readily transmitted from one susceptible host to another, thereby regaining its original invasiveness and virulence. (3) It must be free from other organismal contaminants that might possibly be pathogenic. (4) The vaccine must contain enough antigen to effect an adequate immunizing infection. The optimal range of virus content must be quantitatively controlled. (5) The vaccine must also be qualitatively controlled: the virus must not be attenuated to the point where it ceased to be a good immunogenic antigen. (6) The vaccine must be stable enough to stand up to a variety of adverse conditions without losing its immunogenic capacity. (7) Production methods must be such that the vaccine would not be too expensive for practical use.

After discussing the use of vaccines in yellow fever, rabies, and blue tongue, Dr. Cox spoke at greater length on the prevention of poliomyelitis. Gamma globulin was not the answer to the problem of securing long-term protection against this disease. The only thing to do was to concentrate on developing a safe vaccine which would give a long-term and solid protection against poliomyelitis. He believed that the most logical and practical way to immunize against the disease was to use the natural portal of entry—"the oral route, employing an attenuated living virus under qualitatively and quantitatively controlled conditions." Dr. Cox, whose paper will be published subsequently in full in this *Journal*, ended by saying that a tested, practicable vaccine for poliomyelitis had not yet been produced.

Phages and Genetics

Dr. M. Delbrück, professor of biology of the California Institute of Technology in Passadena, who began his scientific career as a physicist, paid a personal tribute to his former teacher, Professor O. Hahn, the distinguished physicist, who was in the audience. A bacterium infected with one phage particle might, Professor Delbrück said, liberate several hundred bacteriophages twenty minutes later. A phage particle was small compared with other organisms, but large from the point of view of the chemist—of the order of a billion times heavier than a hydrogen atom. The ability to replicate complex molecular structures accurately was the most basic and universal characteristic of living organisms and, from the chemical standpoint, the most obscure. For many reasons the phages provided the most useful material for clarifying this problem. The most exciting discovery in this field was the finding by Hershey and Chase that it was the desoxyribose nucleic acid (D.N.A.) and not the protein in the infecting phage particle that was important: D.N.A. was the genetic material proper. The protein, and perhaps some other "organelles," formed a coat which might be important for protecting the nucleic acid and for getting it into the bacterium: but they did not enter the bacterium. Watson and Crick had complemented this discovery "by important insight into the physical and chemical structure of this material." The gross structure was that of a "one-dimensional tape of great length coiled into a small column." This tape was a duplex of two polynucleotide chains, each of which contained the entire genetic "information." (In a footnote to his paper Delbrück says: "If we say that the genes carry information we do not mean anything new; we merely focus our attention at one aspect of these determiners of organic development: this aspect is the number of possible organic developments, considering the totality of all possible sets of genes, from which the particular set of genes singles out one particular development, by virtue of the specific 'information' contained in it.") After describing work on phages labelled with radioactive phosphorus, Dr. Delbrück said that phages, like higher organisms, had a mechanism for genetic recombination which came into play when two or more related phage particles infected the same bacterium. "It seems rather likely to us that the essential mechanism of recombination in such an encounter between two intracellular phage particles is similar to crossing over during meiosis in higher organisms."

Professor Delbrück then described work on the reactivation of phages previously inactivated by ultra-violet light and ionizing radiation. Infection of bacteria with several damaged virus particles reversed the primary damage by, it was thought, a process similar to genetic recombination "in which the damaged particles pooled their undamaged parts to obtain viable particles." Work on phages which seemed to live symbiotically with the bacterial host in a "prophage stage" in a union that might last through an indefinite number of bacterial generations suggested that in this stage a phage was intimately related with the genetic material of the host. "If this turns out to be true, then an evolutionary descent of the virus from the host can hardly be doubted." Professor Delbrück considered this also implied that damaged phages infecting bacteria obtain replacements from the genetic material of the host.

Towards the end of his description of a highly complex subject Professor Delbrück said: "Our period in biology may be likened to the 1890s in physics, when, with the discovery of radioactivity, of *x* rays, and of the electron, physicists began to realize that the interpretation of macroscopic physics in terms of atoms presented a real possibility and opened entirely new vistas of research . . . we in biology can look forward to as good a time as our colleagues in physics have had these last fifty years."

Conclusion

After the scientific sessions the visitors had the alternatives of visiting the works and laboratories of Farbwerke Höchst A.G. or of listening to a chamber concert of string quartets of Schubert, Haydn, and Mozart. A feast of good food and wine brought the day to an end.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Ion-exchange Resins

SIR,—I have read with interest your leading article on the ion-exchange resins (*Journal*, March 13, p. 633), but I am surprised to find the statement that "it is questionable whether resin treatment should be used at all" in Type II nephritis. Nephrotic oedema is notoriously resistant to treatment, and in the ion-exchange resins we have a new weapon which appears to produce very good results. The fact that these resins are potentially dangerous in the presence of renal failure is no argument against their careful use when renal function is normal. In the uncomplicated case of Type II nephritis there is little more risk than in the normal person of producing severe acidosis, hyperkalaemia, or complications due to increased ammonium absorption. Your leading article mentions a further possible danger, that of causing or aggravating structural damage in the kidney, and this is considered a possibility, because granular casts may occur in the urine even in healthy subjects taking cation exchange resins. If renal function is normal, the urine of patients on the resin is highly acid. Granular casts can readily be found in such acid urine and are not evidence of structural damage to the kidneys. Their occurrence was noted in the highly acid urine of patients treated with sodium mandelate and ammonium chloride, and it was shown that they disappeared when the urine was no longer so acid.[1]

The medical profession is divided on the advisability of using mercurial diuretics in Type II nephritis, for these drugs are known to act by impairing tubular function. Such evidence as we possess at the present time suggests that ion-exchange resins are a very promising form of treatment for nephrotic oedema, and it would be unfortunate if your leading article were taken as a serious warning against their use even in patients whose urea clearance is not seriously impaired.—I am, etc.,

London, W.C.1. M. L. ROSENHEIM.

REFERENCE

1 Rosenheim, M. L. (1936). *Lancet*, 2, 1083.

Pre-operative Anticipation of Thrombo-embolic Episodes

SIR,—In his medical memorandum on a possible method of pre-operative anticipation of thrombo-embolic episodes Mr. John Dutton (*Journal*, March 6, p. 566) makes several interesting points. He states that if it could be foreseen which patients were liable to thrombo-embolic phenomena active measures for their prevention could be taken. The guide for this prophylaxis is to be based on the response of the clotting mechanism to an injection of adrenaline. Unfortunately this test involves the performance of eosinophil counts and clotting times at half-hourly intervals over a four-hour period, which will preclude its universal application to all patients undergoing surgery in a general hospital. If Mr. Dutton has found six cases of post-operative thrombo-embolism in his first 50 cases he has been fortunate in a statistical sense, for the general incidence of such complications must be very much lower. The rational basis for using an accelerated clotting response as a reason for active anticoagulant prophylaxis in an otherwise healthy patient remains unproved.

Waugh and Ruddick,[1] Silverman,[2] and Rosenthal,[3] using sensitized coagulation time tests, have all noted accelerated clotting in patients who showed no evidence of thrombosis. Accelerated clotting (interpreted as a clotting time less than the minimum of a normal range based on 100 controls) has been noted with the heparin-retarded plasma clotting test also in a variety of states with no clinical manifestation of thrombo-embolism.[4] These include acute inflammation post-haemorrhagic states as well as the majority of a series of 40 patients who underwent a group of common operative procedures. On the other hand, of 50 cases of recent thrombo-embolism, 37 demonstrated accelerated clotting.[5] Thus, although it may be deduced that thrombosis is associated with a shortened clotting time the reverse does not necessarily follow.

It is to be hoped that Mr. Dutton's research will produce valuable results in the prevention of these tragic consequences of surgical trauma. However, the danger of reliance on an *in vitro* laboratory test without reference to the clinical state and the all-important vascular factors in thrombosis cannot be allowed to pass unnoticed.—I am, etc.,

Catterick. L. POLLER.

REFERENCES

1 *Canad. med. Ass. J.*, 1944, 50, 547.
2 *Blood*, 1948, 3, 147.
3 *Circulation*, 1952, 6, 257.
4 *Angiology*, 1954, 5, 22.
5 *British Medical Journal*, 1953, 1, 1331.

Anaesthesia in Hospital Breech Delivery

SIR,—I have read with great interest the article (*Journal*, March 6, p. 562) "Anaesthesia in Hospital Breech Delivery" by Dr. R. G. Law and Dr. Shila G. Ransom. The point which interests me chiefly is the statement that forceps on the after-coming head is a procedure which the authors "strongly advocate in all cases." I should like to know the reasons for this. During the time I was in the active practice of obstetrics as a G.P. in the country I never found this procedure necessary. Incidentally, I attended a large number of breech cases and only had one foetal death (if my memory serves me aright), and this was not due to any difficulty in delivery of the head but due to rupture of the cord *in utero* during the manipulations necessary in bringing down extended legs and arms behind the head. This case was during the war, with hostile planes overhead and consequent difficulties, lighting, etc.

All my confinements were done in cottages by the light of a paraffin lamp with an open coal fire. Hence chloroform was the anaesthetic of choice, and it often had to be given by myself, though not when I could get assistance, which was not always and not in the case quoted. Perineotomy was not often practised by me. I heartily approve of it, and wish I had used it more frequently. The method I used for the after-coming head in all cases, without difficulty, was when the baby was born as far as the umbilicus, legs were brought down, unless they were, as was often the case, already delivered, and then both arms were brought down. I then inserted the middle finger of my left hand into the mouth, thus flexing the head. I got the midwife or whoever was present to press on the abdomen just above the pubes to help flex the head, then seizing the legs with a circular swing the head was easily delivered. All my cases with one or two exceptions were delivered in the left lateral position. Needless to say, anaesthesia was always used and, of course, aseptic precautions taken.

I shall be most grateful if Dr. Law would let me know what the advantages of forceps on the after-coming head are. That it is used frequently and successfully I know from experience with reference to a relative of mine.—I am, etc.,

Petworth. DAN C. DRUITT.

Utero-tubal Insufflation

SIR,—Mr. Stanley A. Bond's letter (*Journal*, March 13, p. 646) states that "all the work of Rubin and Sharman is based on the proven fact that the information obtained is definitely attributable to the fallopian tubes alone." I am sure that Rubin and Sharman would not claim that *all* their work is based on this "fact." That it is not a fact is easily shown. Just as good oscillations can be produced by insufflation of a hysterectomy specimen with no peristalsis or spasm visible. The oscillations are just what one would expect of gas passing through a fine tube filled by a sticky medium.—I am, etc.,

Newcastle-upon-Tyne. FRANK STABLER.

The Thyroid

SIR,—In response to requests to amplify my letter (*Journal*, March 6, p. 584) perhaps you will permit me, in the interests of scientific accuracy, to deal briefly with the points raised in the review of my book, *The Thyroid* (February 27, p. 503).

(i) *"There is no reference to controls done, for instance, on post-mortem material from euthyroid patients."*—This is incorrect. A reference to the index would have saved the reviewer from this error. On page 112 I state: "A separate study of the changes in the life history of the normal thyroid gland has led me to add support to the finding that 5 to 10% of apparently normal glands contain collections of lymphoid tissue." The discussion on these controls is then elaborated further. The normal thyroid gland is discussed further on pages 68 and 284, and figures 197 and 198. Even electron microscopy of the normal thyroid in the euthyroid patient is discussed and illustrated (p. 21).

(ii) *"We cannot tell from the tables whether the designated state refers to the patient at the time of the operation or many years previously."*—On page 110, under the title heading "Age," I state: "Taking account only of the age at which the patient presents herself for operation, I find that the diffuse lymphoid hyperplasia or lymphadenoid goitre patient was at operation, on an average, 43 years old, the fibro-lymphoid hyperplasia of Hashimoto 48 years, and the fibrosis of Riedel 56 years." Any further comment becomes unnecessary.

(iii) *"Hypotheses . . . [reading] as statements of fact."*—In such a swiftly advancing subject, speculation is sometimes necessary. Throughout the book I have been careful to indicate any departure from the conventional views. It is not fortuitous, therefore, that both the sentences to which the reviewer, in his penultimate paragraph, takes exception are preceded in the book by "My own interpretation is" (p. 39) and "I would suggest that" (p. 31). Even thyrotropin, in the quotation, appeared in inverted commas in the book to emphasize the uncertainty of its nature and action; similarly the word "collagenin" is qualified in the book as an "unidentified factor" (p. 39).

(iv) *"With regard to the diagnosis of mild toxicity . . . Mr. Levitt's enthusiasm and belief in his thesis have led him to strain fact to fit theory."*—Chapter XIV (p. 186) is almost entirely devoted to the recognition and exclusion of a number of conditions simulating mild thyrotoxicosis; it is emphasized in the book that "instances of mild thyrotoxicosis in this series underwent very strict scrutiny" (p. 198). The clinical data including mild thyrotoxicosis were there also subjected to a critical statistical assessment (pp. 48–59 and 144).

(v) *"We have no idea how the proportion of lymphatic to epithelial tissue was assessed, whether by cell counts or measurement of cellular areas."*—On page 4, I state that "in evolving a reliable criterion for a basic classification I have felt that the final criterion must be the microscopical appearance of the gland." Emphasis is laid throughout on the assessment of cellular areas (pp. 66–77). Nowhere in this book is there any mention whatsoever of cell counts.

(vi) *"We are not told whether the selection of blocks was done on an anatomical basis or on appearance."*—On page 2 it is emphasized that it is "always possible to assess the dominant phase either from the clinical, the macroscopical or microscopical aspect," which was done in selecting blocks of characteristic thyroid tissue. On page 4 I state that "the naked eye view gives a useful, if crude, estimate of the relative quantities of epithelial and lymphoid tissues." The multiplicity of profusely illustrated macroscopic pictures of the gland, seen in the natural state at operation as well as in the formalin-fixed specimen, stresses the importance given to general macroscopical appearance in the selection of the blocks. The danger of an anatomical selection of blocks is also emphasized on page 527.

(vii) *"The patients are designated as mild, moderate, or severe thyrotoxics, but the criteria used to separate the cases studied are not given."*—On page 187 in *The Thyroid* I say: "The assessment of mild, moderate and severe toxicity is often a purely personal problem, necessitating repeated observations of all the stigmata by the same investigator." The paramount importance of a clinical assessment has been stressed throughout the book. Laboratory tests (pp. 188–90), radioiodine tests (pp. 477–93) are shown to help to corroborate the clinical diagnosis especially in a difficult borderline case. So protean have the manifestations of the different degrees of thyrotoxicity been shown to be that hard-and-fast rules have, as indicated in the book, been eschewed.

(viii) *"Nor are we given the average weights of the resected thyroid tissue."*—This desideratum of the reviewer cuts right across the principle of surgical treatment as discussed in pages 388–9, and noted and illustrated on pages 536–7. Its use as a scientific criterion is shown in the book to be outmoded, unnecessary, and of no statistical significance.

—I am, etc.,

London, W.1. T. LEVITT.

Continuous Caudal Analgesia

SIR,—Our experience here of caudal analgesia in disordered uterine function confirms that of Mr. G. Trevor Johnson (*Journal*, March 13, p. 627). May I add a comment in favour of the nylon catheter technique? It is true that nylon tubing has to be obtained by devious means, but it is worth the trouble. In our hands it has reduced the percentage of failures. We sometimes find when the needle seems to have been properly placed that the catheter will not pass beyond its point, or will pass on only half an inch or so. Under these circumstances, continuing with the injection of the anaesthetic solution hardly ever produces satisfactory results. The free passage of the nylon for a few inches beyond the needle-point, on the other hand, is certain confirmation that it is correctly placed. Thanks mainly to this test, we have had only three failures in our last fifty cases.

I agree that polythene is not strong enough and its sterilization unreliable. Nylon tubing can be boiled or autoclaved and used three or four times. It is easier to seal off from the perineum with waterproof plaster than are the hub of the malleable needle and the pressure-tubing. It can be led under a strip of plaster to a more accessible part of the body and end under a sterile dressing, leaving the patient free to move about in bed without displacing it.

The cases in which one fails to place a caudal needle correctly need not be deprived of extradural analgesia; in the three cases mentioned above, one patient had the catheter inserted in the lumbar region through a Tuohy needle, and the other two had between them four lumbar extradural injections of 1/600 cinchocaine with 1/100,000 adrenaline, each injection providing four hours of analgesia.

—I am, etc.,

Cambridge. H. R. YOUNGMAN.

Hibernation Anaesthesia

SIR,—Drs. Frank S. Preston and Hugh Y. Wishart (*Journal*, March 13, p. 645) describe an interesting case as "prolonged hypotension following hibernation anaesthesia." From their detailed description it would appear that it was really a case of shock following inadequate anaesthesia. In our opinion the dosage of drugs used, 12.5 mg. of chlorpromazine, 12.5 mg. of promethazine, and 25 mg. of pethidine, together with an *aliquot* mixture of nitrous oxide and oxygen by inhalation, is unlikely to protect an aged patient from such a severe surgical procedure. It would seem obvious that, as "a few ml. of a 1/250,000 solution of L-*nor*adrenaline" produced a marked rise in blood pressure, the effect of the small dose of chlorpromazine had disappeared. One of the most striking attributes of this drug is its anti-adrenergic action, and at the stage when the *nor*adrenaline was administered a state of shock had supervened. The fact that atropine and neostigmine had no effect supports this view. We feel that if the drugs had been given in adequate dosage to produce "hibernation" anaesthesia this complication would not have arisen.

—We are, etc.,

ANGUS SMITH.
London, N.W.1. J. G. FAIRER.

Methylpentynol

SIR,—Whilst recent contributions to your correspondence columns have dealt chiefly with the use of methylpentynol for premedication, at Warlingham Park Hospital we have been using it for the past nine months as a hypnotic with alcoholic patients. Alcoholics are not infrequently addicted to other drugs as well as to alcohol, or they may become drug addicts when they stop taking alcohol. According to *Alcohol, Science, and Society*,[1] "there is no wholly satis-satisfactory sedative" for the alcoholic. Barbiturates, probably the most widely used sedatives, have recently been alleged to have harmful effects in certain cases when used concurrently with alcohol.[2] So far, no evidence has been produced that methylpentynol itself may lead to addiction.

Methylpentynol has, up to the present, been given to more than 50 alcoholics in this hospital, who received no other sedative or hypnotic drug except myanesin during the day for a few days following admission. On the whole, our experiences with methylpentynol have been not unsatisfactory. Apart from difficulties during the first night, our patients had five or more hours of sleep in the great majority of cases, and woke up refreshed with no after-effects. The dosage varied from 1 to 5 capsules (250 to 1,250 mg.). Whilst onset of sleep has been said to follow administration of methylpentynol usually within one hour,[3] in our patients sleep commonly did not follow until one to two hours afterwards, so that we now give it two hours before bedtime. The minority of patients who experienced wakeful periods during the night stated that even then they felt calm and relaxed under the influence of the drug and consequently went to bed less fearful of possible sleeplessness.

No harmful side-effects or after-effects were noted. Liver and renal function tests and full blood counts, taken repeatedly with patients who took the capsules for longer than a few weeks, failed to show any pathological changes. Most of the patients, however, easily gave up taking the capsules after a few days or weeks, and slept without sedation. No systematic inquiry regarding its use by discharged patients has so far been carried out, but we have not heard that any of them who remained sober have continued taking methylpentynol or any other hypnotic.—I am, etc.,

M. M. GLATT.

Warlingham, Surrey.

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Medical Treatment of Peptic Ulcer

SIR,—Your leading article on the medical treatment of peptic ulcer (*Journal*, March 13, p. 632) is important for the stress it lays on the uncertainty both of aetiology and the effects of treatment. As regards the former and the greatly increased incidence of the condition I often think that insufficient regard may be given to changes of fashion in treatment. We all know now that many of the classical symptoms of chronic nephritis were, in fact, due to the treatment given and not to the disease itself. Lord Horder[1] hinted at the effect of the premature outmoding of sodium bicarbonate for indigestion as a possible factor in the increase of digestive disorders. I have long thought that the sudden suppression of bismuth at the beginning of the last world war may similarly have contributed to the incidence of more serious disease.

Professor Alstead[2] gave reasons for believing that bismuth carbonate was at best a feeble antacid, and Professor Brindle[3] has *in vitro* recently extended and largely confirmed his results. But, though raising the *p*H of the gastric contents will relieve pain, this is far from covering the whole of the complex function of the stomach or the causation of peptic ulcer. Bismuth empirically has been used for digestive troubles for over a century, and it is unlikely that our very acute clinical ancestors were entirely wrong in their observations. Having qualified in 1915 I was a convinced believer in the use of bismuth in 1939 and continued to use it with satisfaction throughout and since the war. One doctor's experience may be of little value, but I must say that I am constantly surprised to find the small number of peptic ulcers I have to treat compared with that of other general practitioners. I do not think this is altogether due to inability to diagnose the condition, for I take full advantage of consultants and *x* rays. I rather think that my continued use of bismuth may have much to do with it.

I have not used the massive doses recommended by some advocates of bismuth therapy, and Dr. Kemp,[4] of Copenhagen, certainly has an impressive list of apparent cures by this method followed up for many years, which you rightly stress is the only useful criterion. I am here more concerned to point out the possible effect of moderate doses in indigestion preventing more serious trouble. It is, in my experience, almost specific in relieving the symptoms of mild appendicitis, but its use is not limited to that.

There are many things we still do not know about bismuth and its effects. It was, for instance, stated by Mr. R. L. Stephens,[5] in the discussion on Professor Brindle's paper, that bismuth will inhibit the digestive action of pepsin at as low a *p*H as 2.0 instead of the usually accepted 4.4. If this is so a new outlook may be given to the use and abuse of "antacids." Certainly there is room for much more research—and research which, from its nature, may be quite outside the usual pharmacological and out-patient fields. They should illuminate what is and has been found in general practice, and, though I would not have general practitioners or professors chasing will-o'-the-wisps, I think treatment might improve and peptic ulcers diminish if our academic brethren kept before them the precept constantly dinned into me at Cambridge—the immense difficulty of proving a negative. This is more true of medicine even than the pure science in which I was taught it.

In writing this I do not overlook the fact that a peptic ulcer may seem to develop quite suddenly, though, as with coronary thrombosis, I fancy this suddenness is more apparent than real and means that the patient has neglected to seek advice for clear premonitory symptoms.—I am, etc.,

W. N. LEAK.

Winsford, Cheshire.

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2 *Lancet*, 1941, 2, 421.
3 *J. Pharm. Pharmacol.*, 1953, 5, 692.
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5 *J. Pharm. Pharmacol.*, 1953, 5*l*, 704.

Danger of Slow Combustion Stoves

SIR,—I think it is important that attention should be drawn to the dangers of installing, without adequate precautions, any of the new forms of slow combustion stove inside a house, whether for cooking food or heating water, if such installation entails the use of an existing chimney.

The danger arises within the chimney, where the gases from the slow combustion eddy and attack the mortar or cement between the bricks, eventually permitting the noxious gases, especially carbon monoxide, to seep into rooms and diffuse throughout the house. The danger to health, as so often pointed out by the late Sir Bernard Spilsbury, comes from the insidious nature of the effects of chronic poisoning from the non-smelling carbon monoxide. He emphasized that there was no distinctive clinical picture associated with chronic monoxide poisoning, but that its effects were to bring out any weakness or idiosyncrasy in the individual, whether respiratory, cardiac, or alimentary.

Recent cases here have redrawn my attention to this genuine danger. The more modern chimneys have to be constructed with an approved lining, but this is not impervious in time to the action of the gases evolved in the process of slow combustion. I am informed by technical experts that the only completely safe protection is a sealed (joint by joint) asbestos stackpipe inside the existing chimney, carried up sufficiently to avoid any risk of equal height chimney pots receiving the gases; in new chimneys the liner

should be a salt-glazed pipe. I have myself not seen any scientific proof of this assertion. It is, however, important that the profession should know of this danger and be warned of the symptoms to which these slow combustion stoves may give rise.—I am, etc.,

Chipping Campden, Glos. C. B. HEALD.

Gastro-intestinal Fuso-spirochaetosis

SIR,—The presence of *Spirochaeta vincenti* and *B. fusiformis* in large numbers in the faeces of patients suffering from diarrhoea and abdominal pain has been reported by the author in 1945[1] and 1947,[2] and its aetiological significance discussed. Subsequent observations have shown that these organisms are commonly found associated with three groups of symptoms: (*a*) Recurrent bouts of diarrhoea at intervals of a few weeks. The patient loses weight and often complains of a peculiar burning sensation in the anal region and rectal mucous membrane. Pain is colicky and severe. The faeces show a *p*H on the acid side—6.0 to 6.6. Arsenical preparations like carbarsone and acetarsol by mouth give relief, but recurrences are common when arsenic is stopped. Penicillin orally gives more lasting relief. (*b*) Acute diarrhoea simulating cholera. These cases go on to dehydration and collapse, and, if not energetically treated with intravenous saline, may end in death. Repeated saline infusions failed to improve the condition of one of them who had anuria. Neoarsphenamine, 0.3 g. in the next intravenous saline, resulted in a quick recovery. These two groups have been fully described in the two earlier papers. (*c*) Pain in the epigastrium. It is often worse after food, not relieved by alkalis, and accompanied by a burning sensation. It is very severe in character and there is tenderness over the area. Vomiting is occasionally present, but does not relieve the pain. Fractional test meal shows total and free acidity within normal limits and the gastric contents show blood and mucus with great regularity. The organisms are present in the gastric contents, though not in the large numbers seen in the faeces of the same cases. There is no diarrhoea, as a rule. Response to arsenicals is immediately good, but the trouble recurs when arsenic is stopped. Penicillin orally is more effective.

Details are given below of a case which has been investigated and followed up over a period of five years. The patient is himself a medical officer. He came under observation in March, 1948, with a history of unbearable pain in the epigastrium for the last two months with occasional vomiting. Previous history included an attack of amoebic dysentery in 1924 treated with a full course of emetine injections, appendicectomy in 1926, and recurrence of diarrhoea with two or three loose motions daily and amoebic cysts in the motion in 1928. Acetarsol tablets orally stopped the diarrhoea and the cysts disappeared. During this attack he noticed acid eructations and "hunger pains" for the first time, both being promptly relieved by alkalis. Subsequently he used to get the hunger pains frequently, lasting for two to three weeks at a stretch. In 1943 he was examined at Madras. Fractional test meal report was "slight increase of acidity, with mucus in all the specimens and blood in the later ones." *X*-ray report: "No evidence of active lesion. Suggestive of healed ulcer." His condition was becoming gradually worse. The usual dietetic and alkaline treatment did not give even temporary relief; in fact, food, especially when hot, aggravated the pain. Tenderness was marked over the area, and he used to roll about in the bed due to the severity of the pain.

In March, 1948, microscopic examination revealed the presence of *Spirochaeta vincenti* in the smears from the gums, in the resting gastric juice, and in the faeces. The gum smears showed *B. fusiformis* also. The saliva and faeces were both on the acid side, the *p*H varying from 6 to 6.6. Repeated examinations of the faeces were made but did not show any evidence of the old amoebic infection. No pathogenic organisms were isolated. A fractional test meal on March 15 showed total and free acidity within normal limits, but blood and mucus were present in all the specimens.

He was started on acetarsol tablets on March 21, 1948. Within a week the pain disappeared and he found he could take a normal diet with impunity. The gum smears and faeces did not show any spirochaetes after March 30, 1948. After a fortnight, when he was no longer taking acetarsol, there was a recurrence of pain. He was then put on a course of penicillin tablets of 50,000 units, one daily for 12 days. Then pain completely disappeared and he has been free for a period of five years—that is, till April, 1953. There was a slight recurrence which made him take another course of 12 penicillin tablets, with the satisfactory results expected. Fractional test meals were repeated on him in June, 1948, and March, 1950. Blood was absent in all specimens on both occasions. The total and free acidity values were within normal limits but higher than in March, 1948, with, however, no pain.

—I am, etc.,

Coonoor, S. India. I. G. K. MENON.

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[2] *British Medical Journal*, 1947, **1**, 948.

Smoking and Mouth Cancer

SIR,—Miss Marion H. Russell, in her interesting article on "Cancer of the Tongue, Mouth, and Pharynx" (*Journal*, February 20, p. 430), puts forward several lines of inquiry to investigate sex differences in prognosis following radiotherapy. While supporting her suggestions, I would add that analysis should be made of the smoking habits of patients with cancer of these organs. "Radium National Form No. 1, Malignant Disease of the Tongue and Mouth," compiled in 1929–30 by the Radium Commission and others,[1] required a note on "Tobacco" for completion of records, showing that an association was recognized or suspected at that time, and much valuable information should be available after 20 years.

Doll and Bradford Hill,[2] in their work to which you refer (p. 445), have jolted us into keeping careful records of the smoking habits of our lung cancer patients, and it seems no less important that we should continue to investigate and record the same information in relation to patients with malignant disease anatomically in closer relation to the cigarette or other source of possible chronic irritation. Prognostic differences which appear to be linked with sex or age could be due, wholly or in part, to differences in smoking habit and/or to duration of smoking.—I am, etc.,

London, W.C.1. PHYLLIS WADE.

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[2] *British Medical Journal*, 1952, **2**, 1271.

"Status Lymphaticus"

SIR,—Risking the charge of levity, may I add to the discussion of this condition the story of a meeting held not long after the first world war, where the anaesthetists were pressing for recognition as such. The plaint was repeated *ad nauseam* that they had no "status." Eventually, a surgeon —was it Sir D'Arcy Power?—rose to say that, while he had the greatest sympathy with the anaesthetists' plea, they had a status not enjoyed by any other members of our profession —that is, the status lymphaticus.—I am, etc.,

Sunderland. W. GRANT WAUGH.

SIR,—I read with bewilderment Dr. H. B. Dodwell's statement (*Journal*, March 6, p. 582) that I have described a syndrome consisting of "anatomical anomalies, recurrent asthma, lymphocytosis, and evidence of the breaking down of the nuclei of lymphocytes" (*Journal*, February 13, p. 398). Like Dr. Dodwell I do not know of such a syndrome, especially as the two last-mentioned findings exclude each other as evidenced by the fact that adrenocortical deficiency is accompanied by lymphoid hyperplasia and lymphocytosis, whereas injection of cortical hormone leads to depletion of the lymphoid stores, lymphopenia, and increased "urinary excretion of uric acid which is presumably formed by the breakdown of lymphatic nuclei." All I did was to draw attention to the obvious similarity between "status lymphaticus" and the state of adrenocortical deficiency to which neither anatomical anomalies nor recurrent asthma nor lymphatic breakdown bear any relationship. I cannot deny, however, that Dr. Dodwell's misrepresentation and lack of understanding have alarmed me.—I am, etc.,

London, W.1. H. UCKO.

Medical Auxiliaries

SIR,—May I be permitted to reply to Mr. S. S. Knight's letter (*Journal*, February 27, p. 520) on the subject of medical auxiliaries? His claim that the training afforded by the Physiotherapists Association is comparable to that of the Chartered Society of Physiotherapy calls for comment. Candidates for training in schools recognized by the Chartered Society must first submit evidence of a standard of education which would enable him/her intelligently to grasp the basic sciences which form the background of treatments by physical methods. Instruction in these essential sciences and their practical application is carried out by experienced teachers, both physiotherapists and members of the academic staff of medical schools, where the emphasis throughout is on education, and facilities are adequate for this purpose. Throughout the whole three years of training, not only is the application of the practical skills acquired by the students to the treatment of patients very carefully supervised, but the students are also under constant guidance and instruction from really experienced teachers. The examinations are searching and thorough, and are conducted by members of the medical profession and teachers of the Chartered Society. Post-registration courses and congresses ensure a maintenance of that high standard of work that has come to be expected of the chartered physiotherapist.

The intensive training in principles over a short period, mentioned by Mr. Knight, is educationally unsound, and the standard of work produced by such "crammed" training is generally inferior to that where adequate time is allowed for absorption. The expression of aims of the Physiotherapists Association is most commendable, but until there is evidence that those aims are really achieved it is perhaps misleading to claim equality of standards.—I am, etc.,

London, S.E.1. S. M. EVANS.

Recruitment of Nurses

SIR,—May we have the advantage of your columns to give a brief account of a scheme for the recruitment of nurses in York, which has been in operation since last September and which shows good promise of success? In conjunction with the education authority a course of evening classes has been organized by the hospital management committee in the nurses' training school of one of our general hospitals for young people of either sex under 18 years who have left school and who are already in full employment in other spheres. The lectures are on a wide variety of subjects which bear on biological problems, medicine, surgery, and nursing care, and are given by consultants, family doctors, the sister tutor, and experts in various ancillary branches of medicine and other social services.

The course is designed to occupy a two-year interval between leaving school and the age of 18, when full training may begin. Lectures, which are loosely integrated in subject matter, are given once a week and are divided up into two winter terms each year, each term of about 13 weeks' duration. The lectures are followed by relaxation with cups of tea and buns, and are interspersed with visits to special departments of the hospital, and with instruction in bandaging, invalid cookery, films, and demonstrations of nursing techniques and discussion periods. By holding the courses in the nurses' training school, the student is brought at once into the atmosphere of the school and into contact with the personnel of the hospital, so that any feeling of diffidence or apprehension on entering may be overcome before the candidate is called upon to make a final decision on whether she wants to enter for a nurse's training or not.

The course was publicized in the local press and by the education authority to school-leavers through the youth employment officers, and to youth clubs, and the response was most enthusiastic—double the number of applicants that could be assimilated being forthcoming. Thirty were accepted, two of whom were boys. The applicants were selected on the following grounds—that they intended to take up a nursing career and that they were physically and mentally fitted to do so. Selection was made by the sister tutor in conjunction with a representative of the education authority, who was in possession of their school records of ability and character.

Enthusiasm for the course has continued unabated, as shown by the attendances, which have been full except when affected by sickness or bad weather. The four girls nearing 18 have all decided to sign on for training as soon as eligible, and from next autumn, when the course starts on its second year, it seems likely that there will be a steady stream of nursing recruits as and when the older ones reach the age of 18. After one year as a pilot experiment it has been decided to plan a second course on exactly similar lines so that both general hospitals will be running similar courses, one starting at the beginning while the other is half-way through. At the same time each course has been planned so that a new entrant could start at the beginning of any one term without feeling the effects of missing the subjects of the preceding term.

The shortage of nurses in training bids fair to be the biggest stumbling block to any plan for the expansion of the hospital service, and in publishing this scheme for a night school for the young people who might take up nursing as a profession we hope that hospitals elsewhere may find in it something of value towards the solution of this pressing problem. The expenses incidental to the course have been largely defrayed by the Ministry of Education, but a great part of the work has been done voluntarily, especially by the sister tutor and by the members of the medical profession, who have given their lectures without fee.—We are, etc.,

A. E. WILLSON-PEPPER.
York. J. K. WILLSON-PEPPER.

Child Life and Health

SIR,—I have read with interest the study presented by Professor Charles McNeil on the above subject (*Journal*, March 6, p. 533). I saw the service grow in my own district almost from scratch (when a voluntary body had charge of it) to present unimagined proportions.

According to Freudian teaching on the psychopathology of mental and neurotic illness in the adult, the seeds of such are laid in the frustration of the biological needs of the infant. The physical aspect of child health is undoubtedly extremely important, and my training in and practice of paediatrics stressed the sensible, though broad-minded, routine of feeding, "potting," sleeping, and playing in the life of the infant in order to produce its health and happiness. In latter years, however, I became interested in the psychological aspect of health and disease, and it seemed to me that it was almost axiomatic that a contented mother had a contented child and that a stable mother had less illness in her family than a harried, worried, fidgety mother. It may be a matter of genetic inheritance that stability breeds stability, but there would seem to be something more involved—an ingredient which ensures that the right food is digested properly, and that the sleep is tranquil, and that the other biological needs are not only satisfied but happily satisfied. That ingredient is not visible; it is an atmosphere of tranquil security which surrounds the infant, setting its mind at rest and ensuring harmonious working of its bodily functions. In other words, the body is dependent on the mind, so that the mental state of the infant is of paramount importance to its physical well-being. Even though the infant mind is not consciously working, it is intensely impressionable.

According to this thesis, therefore, I would suggest that in child health of to-morrow there should be psychiatric sessions attached to each child welfare centre with the specific objective of supportive therapy for the emotionally unstable mother, which would cater also for the needs of the antenatal mother, since much physical and mental trouble is laid up for the offspring during the period of gestation. I would also suggest the great value to child health of the establishment of marriage guidance clinics in the setting of the child welfare centre; at these the man or girl to be married could discuss important premarital problems, and also parents in emotional difficulties might be helped, to the immense benefit of the household and the prevention of much neurotic illness among their children.—I am, etc.,

Morpeth. J. H. THOMPSON.

Emotions and the Nose

SIR,—Personal experience prompts me to offer two observations upon the papers of Mr. P. Reading, Mr. K. Malcomson, and Dr. D. O'Neill (March 6, pp. 552 and 554). Is it really necessary to invoke anything so recondite as physiology and interference with regulation of body temperature to explain aggravation at night? Will not the blanket allergens of wool and bacteria suffice for most people, or even the homely possibility of the horizontal posture affecting mucous membrane blood vessels? Repeated caravan holidays have taught me the value of eating the antihistamine tablet before both the morning and the evening blanket-tossing.

The psychiatric study, although suggestive, suffers inevitably from the absence of controlled observations. Case 10 found that her nose cleared during the excitement of walking out with her boy friend. Mine used to clear regularly under the excitement of visiting my E.N.T. consultant. Could the sneezing of Case 10, while evacuated to the country, have been due to musty hay or any other rustic allergen? This study, as presented, scarcely warrants a more specific conclusion than that "when the investigation of post-war urban Britishers is carried far enough and deep enough, then some frustration or anxiety will usually be uncovered."—I am, etc.,

Doncaster. CEDRIC C. HARVEY.

Herpes Simplex Virus in Infantile Eczema

SIR,—Dr. G. I. Barrow's article on "The Herpes Simplex Virus in Infantile Eczema" (*Journal*, February 27, p. 482) reminds me of two cases which connect with his series.

On August 25, 1953, a 4-months-old baby was vaccinated. A typical vaccinia resulted and the scab had already cleanly separated when her mother—never vaccinated before—fell suddenly ill, on September 17. She showed three vaccinia-like lesions on the edges of the eyelids and a phlyctenular lesion on the sclera of the right eye, with severe cellulitis of the eyelids and cheek and a considerable painful adenitis in the pre-auricular region and neck. She felt ill, she had much pain, and her temperature was 101.2° F. (38.4° C.). She had been suffering from ulcerative colitis, but had no skin conditions. One week later her other child, 18 months old and also never previously vaccinated, developed a large herpetiform eruption in the right groin, again with marked cellulitis and lymphadenitis, fever, etc., followed within a few days by further 5–6 groups of vesicles in the vicinity. Her skin was clear, but she had just recovered from pityriasis rosea. Both cases were treated with systemic penicillin and ung. chloramphenicol; both took over three weeks to recover. There is a slight residual scarring in both cases, and the mother has partial loss of eyelashes.

A third child, 4 years old, had erythema nodosum with strongly positive Mantoux test two years ago.—I am, etc.,

Tutbury, Staffs. J. I. HOFMAN.

Burns and the Adrenal

SIR,—In your annotation of March 6 (p. 572) you spoke of the "gross inadequacy of all methods of assessing the activity of the adrenal cortex." A reliable chemical method suitable for routine use was described to the Heberden Society in December, 1952, and first published in *Nature*.[1] Using a simplified form of the method,[2] a technician can assay six to eight specimens a day. The subject of steroid assays is too complex to discuss in a letter. What matters is that the assay of 17-ketogenic steroids in urine, referred to above, does answer our everyday needs.

Dr. Simon Sevitt's paper (p. 541), with which your annotation is concerned, does little to clarify the indications for cortisone therapy in the treatment of severe burns. There is good evidence that adrenaline will cause a fall in the eosinophil count in the absence of the adrenals, and that intravenous adrenaline does not give rise to an increased output of adrenocortical steroids.[3] It should not be difficult to follow the daily output of 17-ketogenic steroids in severely burned patients and to find out whether in fact adrenal failure is responsible for death in some cases. Alternatively it would be simple to add hydrocortisone or cortisone aldehyde to the transfusion fluids of a controlled series of patients.—I am, etc.,

Sheffield, 3. H. F. WEST.

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2 Gibson, G., and Norymberski, J. K. (1954). *Ann. rheum. Dis.* In press.
3 Sandberg, A. A., *et al.* (1953). *J. clin. Endocr.*, **13**, 629.

SIR,—Dr. Simon Sevitt (*Journal*, March 6, p. 541) seeks to revive the adrenaline test of adrenocortical function. Your annotation (p. 572) appears to support the suggestion implicit in Dr. Sevitt's article that 0.3 mg. adrenaline given intramuscularly or subcutaneously is an adequate adrenal cortical stimulant. The annotation, however, carefully refers to intravenous adrenaline acting on the pituitary to stimulate the production of A.C.T.H. It further refers to three of Dr. Sevitt's patients in whom intravenous adrenaline was ineffective. Dr. Sevitt, however, gave adrenaline to his patients by the intramuscular or subcutaneous route. On p. 543 he quotes evidence that *intravenous* adrenaline produces an increase of adrenocortical activity, and on the next page states that his adrenaline test stimulus consisted of 0.3 ml. of 1 in 1,000 adrenaline *B.P.* injected subcutaneously or intramuscularly. The route of administration is not mentioned thereafter, so presumably all the tests were done as described.

There must be few who regard subcutaneous or intramuscular adrenaline as an adequate adrenocortical stimulus. Dr. Thorn, who was largely responsible for the introduction of both A.C.T.H. and adrenaline as clinical tests of adrenocortical responsiveness, has amplified his earlier views. To quote[1]: "The four-hour A.C.T.H.-eosinophil test is a useful screening procedure in eliminating Addison's disease or acute adrenal failure if a *70 per cent fall* or over is observed. Failure to observe a satisfactory fall in circulating eosinophils must *not* be construed as necessarily indicative of adrenal cortical failure since (1) on occasion A.C.T.H. administered subcutaneously or intramuscularly may be inactivated or destroyed locally, and hence never reach the adrenal; (2) the single administration of 25 i.u. of A.C.T.H. intramuscularly does not place the adrenal cortex under maximum stimulation; and (3) a fall in eosinophils is after all an indirect indicator of adrenal cortical activation in contrast to the measurement of changes in adrenal oxysteroid and 17-ketosteroid excretion. It is also essential to recognize the fact that an initial control level of 100 or more eosinophil cells per c.mm. is necessary if a significant fall is to be detected. Despite these limitations the four-hour eosinophil response to A.C.T.H. remains a useful and highly reliable screening test for the rapid evaluation of adrenocortical responsiveness. These observations refer to the use of A.C.T.H. and *not* epinephrine."

It would be unfortunate if the adrenaline test as now described were to be accepted without further evidence of its validity. In so far as your annotation appears to lend support, it should be withdrawn.—I am, etc.,

Edinburgh. J. A. STRONG.

REFERENCE

1 Thorn, G. W., *et al.* (1952). *Trans. Ass. Amer. Phys.*, **65**, 282.

Diagnosis of Thyrotoxicosis

SIR,—Dr. E. Montuschi (*Journal*, March 6, p. 584) raises the interesting point that sinus arrhythmia is absent in thyrotoxicosis. For some years past this test has been in common use in Dublin for suspected hyperthyroidism. It is a test which is open to certain fallacies. Sinus arrhythmia is more easily elicited in younger patients, and hence the test is less valuable in patients over 50 years of age. In menopausal tachycardia, when, if reliable, it would be very helpful, the results are less satisfactory, as, while its presence is strong evidence against hyperthyroidism, its absence is not so easily interpreted. The value of this and other signs of thyroid disease will be incorporated in a communication at a later date.—I am, etc.,

Dublin. D. K. O'DONOVAN.

Obituary

H. W. MARETT TIMS, O.B.E., M.D.

Dr. H. W. Marett Tims died at Lower Bourne, near Farnham, Surrey, on March 4, eight days before his 91st birthday. All through his professional career his interests ranged widely over the whole field of biology, and he was perhaps best known as professor of biology at the Royal Veterinary College.

Henry William Marett Tims was born at Calcutta, the son of Dr. T. Lamb Tims, and was educated at Reading School and at Edinburgh University, where he had an outstanding career as a student. He obtained first-class honours in anatomy, surgery, and clinical surgery and graduated M.B., C.M. in 1887. Three years later he proceeded to the M.D., with commendation. After graduation he held the appointment of assistant demonstrator in anatomy and physiology in Edinburgh University, and then, in 1889, he came to London to continue his postgraduate studies at St. Thomas's Hospital. Then for a number of years in the late 'eighties and early 'nineties he was employed as a medical officer under the London County Council. In 1892 he became lecturer in biology and comparative anatomy at Westminster Hospital Medical School, an appointment he held until 1901, when he took up a similar post at the Charing Cross Hospital Medical School. A few years later he became reader in zoology at the Bedford College for Women in London University, and in 1908 was appointed to the chair of biology at the Royal Veterinary College. To these two appointments he devoted a good deal of his time until the outbreak of the first world war in 1914, when he relinquished his civilian duties to serve in the R.A.M.C., in which he attained the rank of lieutenant-colonel. For his war work he was appointed O.B.E. in 1919, and in the following year he was awarded the Order of St. Sava by the King of Yugoslavia.

For many years Dr. Marett Tims acted as examiner in physiology and biology for the Society of Apothecaries of London and in elementary biology for the London Conjoint Board. After the war he was for a time reader in zoology and comparative anatomy in London University and lecturer in comparative dental anatomy at the Royal Dental Hospital of London. Always keenly interested in odontology, he contributed a number of important papers on the subject to various scientific publications. He also edited the seventh and eighth editions of *Tomes's Dental Anatomy*. He had been recorder and vice-president of section D of the British Association, and while resident in the Channel Islands, where he lived for a time after the first world war, he was chairman of the Jersey Division of the British Medical Association in 1924–5. In 1888 he married Miss Alice M. M. Findlay, who died in 1950. There was one son and one daughter of the marriage.

Dr. AMBROSE EMERSON, who was in general practice at Eastbourne for many years, died suddenly at his home at Vennes-sur-Lausanne, Switzerland, on January 28 at the age of 78. Ambrose Emerson was born on January 15, 1876, and was educated at Cambridge University and at University College Hospital, graduating M.B., B.Chir. in 1901. He proceeded to the M.D. three years later. He held appointments at the Stanley Hospital and the Hospital for Women, Liverpool, before moving to London, where he worked successively as house-physician at the East London Hospital for Children and as clinical assistant to the ophthalmic out-patients department at the London Hospital. In 1906 he entered a partnership at Eastbourne, where he remained until he retired in 1922, except for the period of his service as a temporary captain in the R.A.M.C. in Italy and France in the first world war. In 1923 he was appointed a cavalier of the Order of the Crown of Italy for distinguished services rendered during the war. In 1922 he took up residence in Switzerland and remained there until his death, except for the major part of the last war, when he was in England. He is survived by a widow, two sons, and three daughters.

Dr. EDGAR STEVENSON, who died at his home at Hoylake, Cheshire, on February 3 at the age of 86, was for many years well known as an ophthalmic surgeon in the Liverpool area. He studied medicine at Aberdeen, graduating M.B., C.M. in 1889, and proceeded to the M.D., with commendation, three years later. After a period of study at Strasbourg he returned to his home at Birkenhead. In 1892 he was appointed house-surgeon to the Liverpool Eye and Ear Infirmary, becoming assistant surgeon two years later, as well as honorary ophthalmic surgeon to Toxteth workhouse. At the beginning of the century he was appointed to the honorary staff of the Eye and Ear Infirmary—to which he later became consulting ophthalmic surgeon—and also demonstrator in ophthalmology in University College, Liverpool, a post he held for a number of years. At Liverpool he was in partnership first with Dr. Edgar A. Browne, a son of Hablot Knight Browne, better known as "Phiz," the illustrator of books by Charles Dickens, and later with Dr. F. B. Chavasse, son of the second Bishop of Liverpool. During the first world war Dr. Stevenson served as an ophthalmic surgeon attached to the 1st Western General Hospital. Later he became ophthalmic surgeon to the Ministry of Pensions Hospital at Liverpool. Among his many contributions to the medical literature was a paper on the treatment of corneal opacities by electrolysis which appeared in this *Journal* in 1896. After his retirement he went to live at Hoylake. For relaxation he enjoyed fishing, and only recently had contributed an article to the *Fishing Gazette*. His wife, formerly Miss Helen D. L. Gunn, had predeceased him by only two weeks.

Dr. G. H. GRILLS, formerly medical superintendent of the County Mental Hospital, Chester, died at his home at Lymm on February 16 at the age of 82. Galbraith Hamilton Grills was born on April 17, 1871, and was educated at the old Queen's College, Belfast, and at Liverpool University, graduating M.B., B.Ch. at the former Royal University of Ireland in 1899. He proceeded to the M.D. in 1902, and was awarded the diploma in mental and nervous disorders of the University and the Gaskell medal and prize of the Royal Medico-Psychological Association. Dr. Grills spent practically the whole of his professional life at the County Mental Hospital, Chester, where he first went in the early 1900's as assistant medical officer. He later became medical superintendent and held the post for many years, retiring in 1945, when he went to live at King's Norton, Birmingham. Last year, however, he returned to the county he had served so well and took up residence at Lymm, where he died.

J. H. M. writes: Having been associated with Dr. Grills for well over 30 years, I find it hard to realize that he has passed on. Somehow I regarded him as one who had discovered the secret of perpetual youth. His unceasing vitality, his boundless enthusiasm, and his boyishness of spirits never suggested that he should grow old, although he lived to the good age of 82. He was a doyen and a pioneer among medical superintendents. All his vigour of mind and body was given whole-heartedly to his life's work, which he loved and in which he spent 45 years of active service. His sympathy, kindliness, and knowledge were ever available to his patients as well as to his junior colleagues, who mourn the passing of a great and lovable gentleman.

He was invariably in the van in the use of new treatments. His hospital was among the first to introduce malarial therapy, diathermy, sun-ray lamps, electric shock treatment, etc. His motto was "To stand still is to recede." He genuinely felt for his patients. My own feeling is that he regarded it almost as an injustice that they should be so sorely afflicted. "What better are we," he used to say, "that we should escape?" Material improvements during his tenure of office were many and included a new annexe (12 wards) with operating theatre, a handsome home for nurses, and the complete modernizing of the (then) 100-year-old building. He had no hobbies as such. He was devoted to his family and home. He was a profound thinker, always seeking after truth. Books dealing with matters metaphysical and mystical were his joy, and it was a sheer delight to listen to his discoursing on these and kindred subjects. From him I learnt much. He is survived by his wife and daughter and three grandchildren, to whom we extend our sympathy in their sudden and sad bereavement.

Dr. C. B. COHEN, a well-known general practitioner at Oxted, Surrey, died in St. Thomas's Hospital on February 10 at the age of 59. Charles Benjamin Cohen was born on August 15, 1894, the son of the late Sir Benjamin Cohen, K.C., and was educated at Rugby School and at Trinity College, Cambridge, before entering St. Thomas's Hospital as a medical student in 1916. He qualified M.R.C.S., L.R.C.P. in 1918, and after holding a house appointment at St. Thomas's served as a captain in the R.A.M.C. in the first world war. After demobilization he obtained further experience as a house-surgeon at his own teaching hospital and as a house-physician at the Brompton Hospital. He graduated M.B., B.Chir. in 1920 and proceeded to the M.D. four years later. After a period of practice at Brighton and at New Malden, Surrey, he became, in 1931, a junior partner in a practice at Oxted, where his father had moved in 1914. He soon established himself as a very competent general practitioner and was appointed surgeon to the local cottage hospital, in which, from the time of his appointment until shortly before his death, he was responsible for a large proportion of the emergency surgical work. He was also lecturer to the local branch of the British Red Cross Society and medical officer to most of the schools in the district. He is survived by his widow, a son, who is a doctor, and a daughter, who is a trained nurse.

J. F. S. writes: Dr. C. B. Cohen, known to a large circle of friends as Charles, will be badly missed, as he was a very conscientious doctor, nothing ever being too much trouble: he was always available and good at relieving the anxieties of relations. These were his great characteristics—his competence and his conscientiousness—and he will long be remembered in Oxted and Limpsfield for them.

Dr. U. W. N. MILES died at his home at Bewdley on February 11 at the age of 82, and the borough has lost a well-loved figure and a doctor of the old school. Born at Farnworth, Lancashire, on January 22, 1872, Usher William Newton Miles was the son of a country parson. After leaving Rossall School he became a student at King's College Hospital, London. In 1896 he qualified M.R.C.S., L.R.C.P., having been trained by such men as Burney Yeo, Rose, Carless, and Frederick Silk. After holding resident appointments at various hospitals he became assistant to his uncle, H. L. Miles, at Kidderminster, where he remained until he bought a Bewdley practice in 1901. From that date until his retirement in 1946 he was in general practice, coupling with it the appointments of medical officer of health of the borough, a post he held for 45 years, and honorary anaesthetist at the Kidderminster and District General Hospital, an appointment which spanned the years 1917 to 1946. Being a man of broad mind and wide interests, Dr. Miles did not let himself get into a rut of professional life. For a time he was interested in the Church Lads' Brigade, and in 1909 he started the Boy Scout movement in Bewdley, remaining an active scouter until 1914. At the end of the first world war he was made president of the newly formed local association of Boy Scouts, a post which he filled with great pride to himself and to everybody else's great satisfaction until his death. He was also a keen sportsman, being a good shot and fisherman, a life member of the local rowing club, and a founder member of the tennis club. In quieter vein he was fond of gardening, showing special interest in the growing of chrysanthemums. In his heyday Dr. Miles was a tall, well-built man, and his character fully matched his physical stature. Forthright and plain spoken, he had all the courage of his convictions, but nobody suffered hurt thereby. His was a deeply religious nature, and this brought all the gentleness and goodness of religion into his activities and his dealings with his fellow men. Indeed, he was built four-square. And all these attributes, welded with a sound professional skill and wisdom, made him what he was—a family doctor *par excellence*. To his widow, after the joy of a golden wedding anniversary, his children, and his grandchildren must go the sympathy of all who knew him. —C. P. P.

Dr. D. B. KENNY died on February 13, in a motor accident, at the age of 34. Douglas Boal Kenny was born on February 1, 1920, and was educated at Campbell College, Belfast, and at Queen's University, where he graduated M.B., B.Ch., in 1945. After graduation he held appointments as house-surgeon at the Belfast City Hospital and the Dreadnought Seamen's Hospital, London. A period as a ship surgeon followed before he joined Dr. J. G. Johnston in practice at Lisburn, Northern Ireland. A quiet and kindly man, Dr. Kenny was rapidly building up a reputation as a first-class general practitioner, and he will be greatly missed by his friends, colleagues, and patients. He is survived by his widow, to whom we extend our sympathy.

Dame GRACE THYRZA KIMMINS, who devoted her life to the care and training of crippled children, died on March 3 at the age of 83. Many who benefited by her help and encouragement and the training she was able to provide will feel a sense of personal loss by her death. From the time of her own girlhood the sight of the neglected poor, the blind, and the crippled child had inspired in her a feeling of deep compassion and a longing to help. The Heritage Craft Schools and Hospitals at Chailey, in Sussex, although now incorporated in the National Health Service, is a fitting memorial to her and to the work she undertook so willingly, work which was spread over two generations. She was the founder of the schools, and the children received from her all the devoted and loving care that could be desired. Dame Grace Kimmins opened the first hospital school for cripples at Chailey in 1903, but such an establishment must have been in her mind much earlier when, in 1894, she convened a meeting which resulted in the foundation of the Guild of Brave Poor Things. It was from the guild that seven boys were drawn to become the first inmates at Chailey, and they were housed in old buildings already condemned. Forty years later the school was accommodating more than 500 boys and girls in modern buildings. This magnificent result was achieved through the remarkable determination of a remarkable woman. In her work she had the whole-hearted support of her husband, Dr. C. W. Kimmins, whom she married in 1897, and who was chief inspector of the education department of the London County Council from 1904 to 1923 and deputy vice-chancellor of London University in 1933–4; he died in 1948. The work at Chailey received support from people in all walks of life, from royalty downwards. It had the approval and encouragement of the late Queen Mary, and other members of the Royal Family have honoured the school with their patronage. Dame Grace Kimmins was appointed C.B.E. in 1927 and promoted Dame Commander four years ago.

Dr. JAMES BRYAN HERRICK, the distinguished American cardiologist, died in Chicago on March 7 in his ninety-third year. He was born at Oak Park, Illinois, and spent four years as a school teacher before beginning an association

with Rush Medical College which lasted from 1886 until his death. He graduated in medicine at Rush in 1888, and served as instructor in medicine (1890–4), adjunct professor (1894–1900), professor (1900–27), and finally professor emeritus. He was attending physician at the Presbyterian Hospital, Chicago, from 1895 until he died. In 1910 Herrick was the first to describe sickle-cell anaemia, which he had observed in a negro six years before. In 1912 he published what has become a classical account of coronary thrombosis with myocardial infarction, diagnosed during life; he also showed that sudden coronary occlusion need not always terminate fatally. Besides making numerous contributions to the periodical literature, he was the author of a *Handbook of Medical Diagnosis* (1895), *A Short History of Cardiology* (1942), and an autobiography, *Memories of Eighty Years* (1949), which reflects the kindness, sympathy, and leadership which made him such an outstanding teacher. He was founder and first president of the Chicago Society of Medicine, president of the Institute of Medicine of Chicago, and, in 1927, president of the American Heart Association, which presented him with the Gold Heart Award in 1951. He was also awarded the Kober Medal of the Association of American Physicians in 1930 and the Distinguished Service Medal of the American Medical Association in 1939. *Circulation*, the journal of the American Heart Association, published a special number in honour of Herrick in 1950. A tribute he paid to Nathan Smith Davis might equally have been said about himself: "Men succeed because of native ability and in small measure because of chance, but chiefly through hard work, through a knowledge of their special vocational subject, and through their ability to apply this knowledge."

Medico-Legal

INJECTION INTO ARTERY

Fulham and Kensington Hospital Management Committee in the Queen's Bench Division on March 18 accepted liability for negligent treatment of a patient's fractured left forearm at Fulham Hospital in 1948. Mr. Justice Pearce awarded £8,254 damages, with costs, to the patient, Mr. Ernest Sidney Peters, a 50-years-old Thames waterman and lighterman.

Mr. Peters's complaints were that during an operation for resetting the arm the anaesthetist, Dr. M. R. Rifaat, injected thiopentone into an artery instead of a vein; when a remedial injection of heparin caused swelling of his left arm the plaster cast was not removed until too late, causing the onset of Volkmann's ischaemic contracture; the fracture was set in the wrong position; and all these matters were concealed from him, thus depriving him of an opportunity to seek other medical advice.

Mr. Peters also sued Mr. J. L. Temple, surgical registrar at the hospital in 1948, who was in charge of the operation, and R. G. Odell, Ltd., of Walton Bridge, Shepperton, Middlesex, owners of the Thames barge *Magpie*, on which he was working a winch when his arm was fractured. Both these defendants were dismissed from the suit without costs.

Mr. Peters's case was that he suffered a fracture of the left radius on October 12, 1948. The same evening Mr. Temple was in charge of an operation for setting the arm at Fulham Hospital. Mr. Peters was given an injection of thiopentone in his right arm, but during the operation it was discovered that the anaesthetist, Dr. Rifaat, had injected into an artery instead of a vein. As the effect of thiopentone was to coagulate the blood there was a danger of thrombosis developing and a crisis was created. Mr. Temple recollected reading an article describing what should be done in such a situation. He sent for the article, and, following its advice, the patient was injected with heparin. The heparin accentuated the bleeding around the muscles of the left arm caused by the manipulation of the bones in setting. As soon as it was injected, the plaintiff contended, the plaster ought to have been removed. Although the arm swelled that evening and was extremely painful, the plaster was not removed until another doctor arrived at 11.30 the next morning and advised its removal at once. The damage had then been done.

The bones were said to have been set out of alignment, so that when Mr. Peters saw an orthopaedic surgeon in May, 1949, the arm had to be plated permanently in that position. Everybody agreed that the hand was now completely useless and that Mr. Peters would be better off without it.

Heroic Measures

Giving evidence for R. G. Odell, Ltd., and the plaintiff, Sir Hugh Griffiths, consultant surgeon, said it was imprudent to leave the plaster on the fractured arm after the injection of heparin. In his view, by the time the plaster was removed much of the muscle fibre was already dead. Certain orthopaedic treatment might have prevented some of the deformity, but it was impossible to say that any useful function could have been restored. He did not think the condition of Mr. Peters's arm could have been brought about by arterial spasm following the fracture itself. He agreed that the crisis caused by the injection into an artery called for "heroic measures." The surgery on the right arm was brilliant. In the circumstances, he did not think the failure to remove the plaster was negligence, though it was an error of judgment. He also agreed that the malalignment of the bones occurred some days after the operation and was not the result of faulty work by Mr. Temple.

Dr. O. H. Belam, a consultant anaesthetist, said in evidence that no competent anaesthetist should inject thiopentone into an artery if he was careful.

Mr. St. John Dudley Buxton, consultant in orthopaedic surgery, gave evidence on behalf of the management committee. His opinion was that the condition of Mr. Peters's arm was due partly to arterial spasm following the original blow and partly to manipulation of the bone in setting. No one could say to what degree one factor or the other was responsible for the condition. He considered that everything necessary to produce ischaemic contracture was present in the arm before the anaesthetic injection was given and the arm was placed in plaster.

Parties Come to Terms

At a resumed hearing Mr. Gerald Gardiner, Q.C., for the plaintiff, told his lordship that the parties had come to terms. He said: "When something goes wrong in a hospital it is not easy for the patient to tell what has gone wrong, and naturally he can only place the blame where he sees it. In these circumstances, apart from allegations made against the anaesthetist and others who later treated my client, he also complained that the surgeon, Mr. Temple, who manipulated the limb under an anaesthetic, should, in view of an injection of heparin, have at once removed the plaster. Having had an opportunity of hearing the evidence which has so far been given, I should like to withdraw that allegation." The hospital management committee had accepted liability for everything the plaintiff had suffered, including the original injury by the winch. His lordship would be asked, however, to assess the damages which should be paid to Mr. Peters.

Commenting that this was a very just result, the judge assessed damages at £6,000 in addition to special damages of £2,254.

The Medical Defence Union instructed Messrs. Hempsons, solicitors, to act for Mr. Temple.

RETICENT HOSPITAL

Recently a patient claimed damages from a hospital management committee and house-surgeon for injuries received when a hypodermic needle broke in his back during a lumbar puncture examination. The defendants contended

that the patient had received the correct treatment but had jerked suddenly when the needle was inserted, although he had been fully warned what to expect. The judge accepted the defendants' version, found no negligence or lack of skill on the doctor's part, but made no order as to costs. He added: "I have certainly not overlooked the reticence of the hospital authorities in reporting back to the patient's doctor. They had everything to gain and nothing to lose by frankness at that stage. Instead they remained for a time silent. If I had drawn an adverse conclusion from this they would have had only themselves to blame."

Medical Notes in Parliament

Smoking and Cancer of Lung

Mr. J. R. BEVINS, Parliamentary Secretary to the Ministry of Works, replying on behalf of the Lord President of the Council, whom he represents in the Commons, stated on March 16 to Lieutenant-Colonel M. Lipton that the tobacco companies' offer of £250,000 for investigation into the relationship between smoking and lung cancer was accepted by the Medical Research Council at its meeting on February 19. The donation would be made available to the Council in seven equal annual instalments, the first of which had been received.

Lieutenant-Colonel LIPTON asked how this money would be spent, in view of the Minister's previous assurances that research had never been hampered by lack of funds. Mr. BEVINS said the work of the Medical Research Council was already subsidized to the extent of £15,000 a year by the Department of Scientific and Industrial Research. That was additional to the £35,000 a year from the tobacco companies, and there was a total of about £400,000 spent on cancer as a whole by the Medical Research Council. Dr. STROSS said the original statistical work by the Medical Research Council, conducted by Dr. Doll and Professor Bradford Hill, cost only £7,000, and was a magnificent piece of work which showed where the problem lay. This additional sum should be welcomed, because it should prove ample for all the further work needed to elucidate the problem.

Cancer Registrations

Mr. N. DODDS asked the Minister of Health on March 18 what progress had been made in ensuring the complete registration of all cases of cancer. Mr. IAIN MACLEOD informed him that effective registrations of new cases in hospitals in England and Wales, which were 23,239 in 1945, 40,333 in 1947, and 49,110 in 1948, were expected to be about 58,000 for 1953. This figure was estimated to be about half the total probable number of new cases of cancer in 1953 in England and Wales. He had recently issued a circular encouraging hospitals to make still greater efforts to achieve the registration of all cases, and had asked for progress reports by June 30.

Mr. DODDS asked whether the records were kept on a voluntary basis or a compulsory basis; and, if voluntary, why. Mr. MACLEOD said that it was still being done on a voluntary basis. He had recently been advised by the Standing Advisory Committee that, for a variety of complicated reasons, it was best that it should continue on a voluntary basis.

Air Pollution Report

Mr. ERNEST MARPLES, Parliamentary Secretary, Ministry of Housing and Local Government, answering a number of questions on March 16 about air pollution, said that he understood the Beaver Committee expected to present a further report before the end of the summer. The committee's interim report contained a clear statement of the main facts at present known about air pollution and the preventive measures already in operation, and he asked the M.P.s to await its next report on possible further action. The Minister had, however, just received from the committee some interim recommendations about the need for fuller measurements of air pollution and for extended research into pollution by sulphur compounds. These were being studied. The committee was already in close touch with the Medical Research Council about the influence of air pollution on human health. The Minister believed that the creation of smokeless zones in suitable areas had a useful part to play in reducing air pollution, and had recently assured the local authorities who possessed the necessary powers of his readiness to consider proposals for further smokeless zones.

Prescribing Costs

Mr. A. BLENKINSOP asked on March 18 when the Minister of Health expected to introduce area averages of prescribing costs in England and Wales, in view of the commencement of a similar scheme in Scotland. Miss PAT HORNSBY-SMITH, the Parliamentary Secretary, stated that the matter was under discussion with the chemists and with the Joint Pricing Committees, and the Minister was not yet able to give a date. Mr. BLENKINSOP said that they were sufficiently far forward with pricing to make this a reasonably practical proposal. Did the Minister appreciate the importance of giving the extra responsibility to doctors to check their own prescribing costs as probably one of the best ways of keeping costs down? Miss HORNSBY-SMITH said that she recognized that, but it was essential to clear arrears first before starting on a new and complicated scheme.

Miss PAT HORNSBY-SMITH supplied Mr. SOMERVILLE HASTINGS on March 18 with the following figures of the Health Service prescriptions dispensed by retail pharmacists and chemist contractors supplying appliances in successive years since 1949:

Year	Total Cost	Average Cost per Prescription
1949	£30,331,303	36·04 d.
1950	£34,804,535	38·47 d.
1951	£41,662,354	43·91 d.
1952	£43,768,599	48·63 d.
1953 (first six months) ..	£23,898,821	49·15 d.

Flour Improvers

Dr. BARNET STROSS asked the Minister of Food on March 15 whether he could make a statement on the change-over from agene to some other substance as a flour improver; and what were the substances that had been investigated. Major LLOYD-GEORGE replied that he understood that the Medical Research Council had reported on the tests carried out on certain flour improvers. Its report would be considered by the appropriate subcommittee of the Interdepartmental Standing Committee on Medical and Nutritional Problems, and he must await its recommendations. The following were the methods of improvement which had been investigated: agene, chlorine dioxide, the aeration process, ascorbic acid, and potassium bromate.

Prison Treatment of Sexual Offenders

Sir DAVID MAXWELL FYFE, the Home Secretary, was questioned by Mr. LESLIE HALE about the treatment in prison of persons convicted of sexual offences. He replied on March 16 that prisoners convicted of offences of a sexual nature were specially investigated by prison medical officers, who were instructed to recommend for psychiatric treatment those likely to prove susceptible to it. A prisoner would not benefit by such treatment unless he had a sincere desire for it and a genuine anxiety about his condition. Such adverse factors as low intelligence, advancing years, and a history of persistence in the commission of offences reduced the number of suitable cases. In England and Wales there were three centres—Wakefield, Wormwood

Scrubs, and Holloway—to which selected prisoners were sent to receive special treatment from visiting psychotherapists. The precise nature, extent, and duration of treatment in a particular case were determined by the doctor carrying out the treatment. The forms of treatment used included both individual and group methods, assisted, as occasion required, by special procedures. There was also treatment of a less formal kind, especially in training establishments, in which the medical officer played a valuable part as a member of a team. The numbers of prisoners convicted of offences of a sexual nature who were under regular treatment by a visiting psychotherapist for a period exceeding six months in the years 1951, 1952, and 1953 were 25, 26, and 27 respectively. He would hesitate to speak of cure in homosexual cases, and any attempt to give figures of supposed cures could only be misleading.

Vital Statistics

Week Ending March 13

The notifications of infectious diseases in England and Wales during the week included pneumonia 755, scarlet fever 1,476, whooping-cough 2,093, diphtheria 22, measles 2,213, dysentery 1,001, acute poliomyelitis 22, paratyphoid fever 96, and typhoid fever 2.

Infectious Diseases

The largest variations in the trends of infectious diseases in England and Wales during the week ending March 6 were increases of 350 for measles, from 2,099 to 2,449, and 97 for dysentery, from 910 to 1,007, and decreases of 160 for acute pneumonia, from 869 to 709, 84 for scarlet fever, from 1,463 to 1,379, and 64 for whooping-cough, from 2,098 to 2,034.

The largest rises in the incidence of measles were 239 in Norfolk, from 396 to 635, 101 in Cumberland, from 119 to 220, and 52 in Staffordshire, from 207 to 259; the only large decrease in incidence was 59 in Kent, from 94 to 35. The largest variations in the trends of scarlet fever were a rise of 27 in Yorkshire West Riding, from 163 to 190, and a fall of 31 in Lancashire, from 187 to 156. The chief features of the returns for whooping-cough were a rise of 39 in Derbyshire, from 35 to 74, and a fall of 40 in Kent, from 114 to 74. 34 cases of diphtheria were notified; these were 23 more than in the preceding week and were the largest total for the past 67 weeks. The largest rises were from 4 to 10 in Lancashire (Liverpool C.B. 9), from 0 to 5 in Durham (Stockon-on-Tees M.B. 4), from 0 to 3 in Devonshire (Plymouth C.B. 3), from 0 to 3 in Oxfordshire (Henley R.D. 3), and from 1 to 4 in Staffordshire.

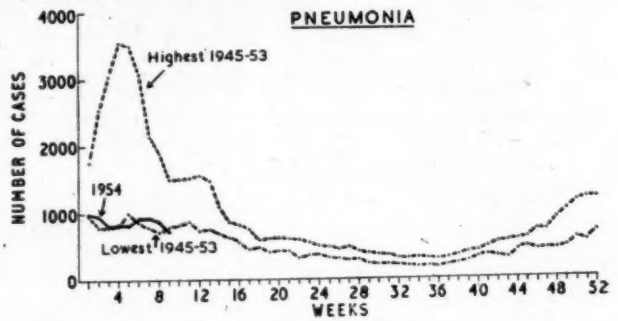
The notifications of paratyphoid fever increased from 5 to 15. This rise was contributed by an outbreak with 11 notifications in Glamorganshire (Cardiff C.B. 7, Penarth U.D. 3, Swansea C.B. 1).

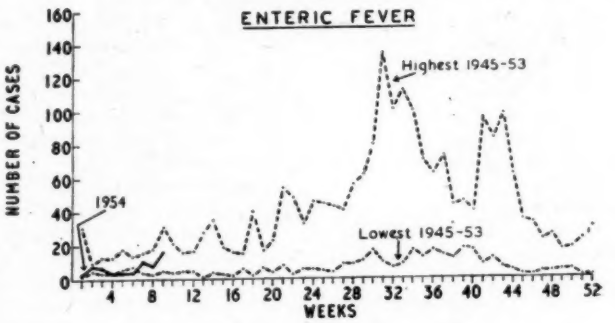
The number of notifications of dysentery reached the highest level for nearly three years. The largest rise during the week was 89 in Lancashire. The largest centres of infection were Lancashire 324 (Eccles M.B. 97, Bolton C.B. 56, Preston C.B. 43, Ormskirk U.D. 33, Liverpool C.B. 23, Salford C.B. 18), Yorkshire West Riding 124 (Leeds C.B. 38, Keighley M.B. 34, Bradford C.B. 15, Royston U.D. 12), London 94 (Islington 23, Finsbury 11, Hackney 10), Middlesex 71 (Enfield U.D. 21, Ealing M.B. 12), Leicestershire 64 (Leicester C.B. 60), Essex 58 (Walthamstow M.B. 17), Staffordshire 58 (Cannock U.D. 46), Kent 37 (Tonbridge R.D. 19), Surrey 25 (Chertsey U.D. 10), Norfolk 24 (Norwich C.B. 24), Gloucestershire 22 (Bristol C.B. 21), and Warwickshire 20 (Birmingham C.B. 19).

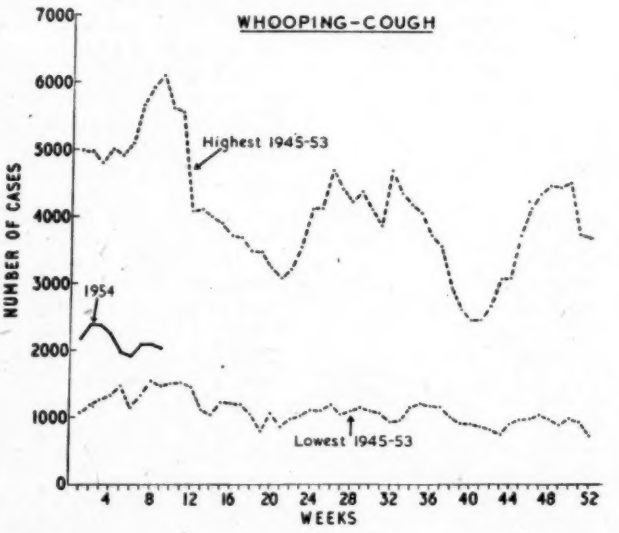
The notifications of dysentery in Scotland are the largest for three years. During the week the largest centres of infection were Glasgow 179, Edinburgh 35, Lanark county 29, and Dundee 16.

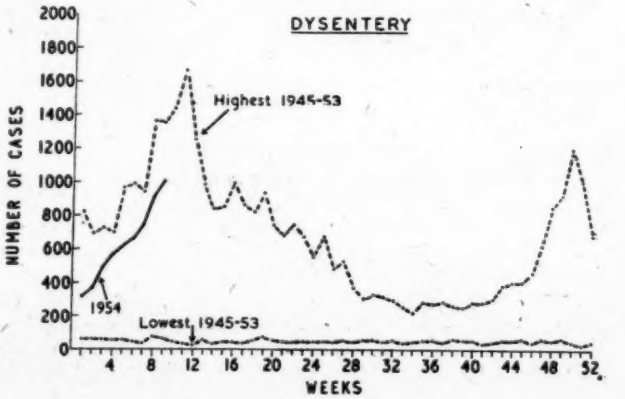
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ———. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 6** (No. 9) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrar-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	34	1	7	0	1	22	1	8	0	4
Dysentery	1,007	94	276	12	5	289	39	97	0	5
Encephalitis, acute	5	0	0	0		8	1	0	0	
Enteric fever:										
Typhoid	1	0	0	0		6	1	1	0	
Paratyphoid	15	1	1	0		6	0	0	0	
Food-poisoning	194	12		0		183	24		0	
Infective enteritis or diarrhoea under 2 years				12	32				9	24
Measles*	2,449	33	82	19	395	27,638	1621	465	135	369
Meningococcal infection	27	3	17	0		35	6	17	1	2
Ophthalmia neonatorum	24	0	2	1		42	3	7	0	
Pneumonia†	709	31	254	9	2	1,301	55	387	21	23
Poliomyelitis, acute:										
Paralytic	14	1	4	0		12	1	3	0	4
Non-paralytic	4	0				5	0			
Puerperal fever§	241	39	12	0		265	55	11	2	
Scarlet fever	1,379	51	181	40	33	1,534	83	202	32	58
Tuberculosis:										
Respiratory	740	109	150	21				157	31	
Non-respiratory	128	7	23	3				33	3	
Whooping-cough	2,034	94	385	45	44	2,758	187	278	26	87

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	1	1	0	1	0	0
Dysentery	0	0		0		2	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	15	1	1	1	3	15	6	4	2	1
Influenza	26	1	2	0	0	193	19	10	3	5
Measles		0	0	0	0		0	1	0	0
Meningococcal infection		0	0				0	0		
Pneumonia	323	51	28	10	5	469	72	28	17	9
Poliomyelitis, acute	1	0			0	2	0			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	129	17	18	4	6	134	10	16	2	7
Non-respiratory		1	1	0	2		4	3	2	0
Whooping-cough	3	0	1	0	0	3	0	2	0	0
Deaths 0–1 year	275	28	28	5	15	244	25	24	14	18
Deaths (excluding stillbirths)	6,457	868	707	125	201	6,706	915	721	159	207
LIVE BIRTHS	8,009	1181	904	227	399	7,861	1173	864	197	485
STILLBIRTHS	207	23	26			199	23	27		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

New Chair of Anaesthetics.—Dr. W. W. Mushin has been appointed as the first holder of a new Chair of Anaesthetics in the University of Wales. Dr. Mushin qualified in 1932 from the London Hospital, and was then for a time first assistant in the Nuffield Department of Anaesthetics at Oxford. In 1947 he became director and lecturer in anaesthetics at the Welsh National School of Medicine, Cardiff, his present appointment. He is also adviser in anaesthetics to the Welsh Regional Hospital Board. In 1948 he was elected F.F.A. R.C.S.

Faculty of Anaesthetists' Dinner.—The Faculty of Anaesthetists of the Royal College of Surgeons of England held its sixth anniversary dinner in the library of the College on March 17. The Dean, Dr. Bernard Johnson, presided, and among the guests were the High Commissioner for South Africa, the High Commissioner for Ceylon, the Acting High Commissioner for the Federation of Rhodesia and Nyasaland, Sir Russell Brain, P.R.C.P., Sir Cecil Wakeley, P.R.C.S., Mr. A. A. Gemmell, P.R.C.O.G., Sir John Charles, Chief Medical Officer of the Ministry of Health, Sir Philip Morris, Vice-chancellor of the University of Bristol, Sir Gordon Gordon-Taylor, and Dr. G. Godber. Sir John Charles proposed the toast of the Faculty, and in his acknowledgment Dr. Johnson reviewed the year's work and particularly the educational aspects of it. He referred with gratitude to the gift of £1,000 which the Faculty had received from the Association of Anaesthetists to start a foundation fund for the proposed department of research. The health of the guests was proposed by the Vice-dean, Dr. T. Cecil Gray, and replied to by Sir Philip Morris.

Centenary at Queen's University, Ontario.—In February, 1854, at the home of Sir John A. Macdonald, the father of confederation in Canada, plans were laid for a Faculty of Medicine in the 13-year-old Queen's University at Kingston, Ontario. The centenary is commemorated by a special issue of the *Canadian Medical Association Journal* (the March issue) which has on its cover the armorial ensigns of the university. Inside, all the scientific articles have been contributed by members of the teaching and research staff, and there is a guest editorial by Dr. Austin Smith, editor of the *Journal of the American Medical Association*, who is himself a graduate of Queen's. Queen's University was established by a Royal Charter issued by Queen Victoria in 1841, its foundation being sponsored by the Presbyterian Church of Canada, which remained its legal owner for 71 years. Since 1913 there has been a corporation of trustees, staff, graduates, and benefactors, which receives substantial support from the government of Ontario and, more recently, Ottawa. There are some 4,000 students, of whom about one-tenth are medical.

Professorial Appointments at Sheffield.—Dr. D. H. Collins has been appointed to the Chair of Pathology at Sheffield in succession to Professor H. N. Green. Dr. Collins graduated from Liverpool in 1930, where he was subsequently junior lecturer in pathology. In 1934 he was appointed first Rheumatism Research Fellow in the University of Leeds. During the war Dr. Collins was in the Emergency Pathological Service. In October, 1946, he returned to Leeds as reader in clinical pathology, his present appointment. Dr. Collins is especially interested in diseases of the bone, and he has published a book on spinal disease. He is an assistant editor of the *Journal of Pathology and Bacteriology*. Professor Green has gone to Leeds to take up the Chair of Experimental Pathology.

Another professorial appointment at Sheffield is that of Dr. G. M. Wilson to the Chair of Pharmacology and Therapeutics, which becomes vacant at the end of this month as a result of Professor E. J. Wayne going to Glasgow as Regius Professor of the Practice of Medicine. Dr. Wilson graduated at Edinburgh in 1940, obtaining the M.D. with gold medal in 1950. During the war Dr. Wilson was in the

medical branch of the R.A.F., where he was a medical specialist. In 1947 he became an assistant to the medical unit at St. Mary's Hospital, London, and in 1950 went to Sheffield as lecturer in therapeutics. During 1952–3 he held an Eli Lilly travelling fellowship at Harvard University. Dr. Wilson's main publications have concerned the peripheral circulation and the part played by hormones in metabolic and cardiovascular disorders.

Silliman Lectures.—This year's Silliman Lectures at Yale University mark the fiftieth anniversary of the famous series given by Sir Charles Sherrington in 1904 which culminated in his classic *The Integrative Action of the Nervous System*. The lecturer this year is Professor Ragnar Granit, from Stockholm, whose subject is "Receptors and Sensory Perception." The lectures will be given on April 29 and 30 and May 3 to 7.

Vade-mecum on Transfusion.—*Notes on Transfusion*, a pamphlet intended primarily for the junior medical staff of hospitals, has been revised and reprinted. It is issued by the Ministry of Health on behalf of the National Blood Transfusion Service, and is distributed free of charge by regional boards and transfusion centres. In 16 pages the pamphlet gives concise and practical advice on the main difficulties that a houseman is likely to encounter. It deals with choice of fluid; storage of blood and plasma and criteria of fitness for use; volume and rate of transfusions; blood grouping and compatibility testing; administration of transfusions; transfusion records; complications and dangers of transfusion; investigation of transfusion reactions; and, lastly, the Rh factor.

Grants for Research at the Tavistock Clinic.—Dr. John Bowlby's work on the effects of separating young children from their mothers is receiving financial support from the following organizations: Trustees of Elmgrant (a private British fund—£1,650), European Office of W.H.O. in conjunction with the International Children's Centre, Paris (£3,900), and the Josiah Macy Jr. Foundation (£3,900 per annum for three years). The Foundations Fund for Research in Psychiatry (U.S.A.) has made a three-year grant of approximately £2,000 a year to Dr. H. Ezriel for research on analytic technique. Both Dr. Bowlby and Dr. Ezriel are working at the Tavistock Clinic, London.

Royal College of Surgeons in Ireland.—At the annual general meeting of the Association of Graduates, Royal College of Surgeons in Ireland, which was held recently in the College, the following officers were elected for the year 1954–5. *President:* Dr. J. D. H. Widdess; *Vice-President:* Dr. J. Lewis; *Hon. Secretaries:* Dr. P. C. D. MacClancy and Mr. T. O'Grady; *Hon. Treasurer:* Dr. D. Riordan.

Readerships at the Royal Free.—London University has announced the following appointments to University readerships tenable at the Royal Free Hospital School of Medicine: Dr. D. N. Baron to the readership in chemical pathology; and Dr. Eleanor J. Zaimis to the readership in pharmacology.

Family Doctor.—The April *Family Doctor* is now out. The main medical articles are on air travel (Sir Harold Whittingham), tuberculosis (by the secretary-general of the National Association for the Prevention of Tuberculosis, Dr. Harley Williams), hypertension (a continuation of Dr. W. C. Alvarez's series), hysterectomy ("There Need be No Fear about Hysterectomy"), blood transfusion—questions answered by Dr. R. A. Zeitlin, and the sensible use of the clinical thermometer (Dr. W. Edwards). The cover picture of a little girl in her bath is one of the best so far.

Sir Russell Brain, P.R.C.P., is to receive the honorary degree of D.C.L. of Durham University at Newcastle on July 3.

Dr. C. E. Dent, reader in medicine at University College Hospital Medical School, London, has been elected a Fellow of University College.

Mr. Michael Harty, F.R.C.S., has been appointed assistant professor of anatomy in the Graduate School of Medicine, University of Pennsylvania.

COMING EVENTS

Professor D. M. Dunlop will deliver the Lumleian Lectures on April 6 and 8 at 5 p.m. at the Royal College of Physicians. His subject will be "The Complications of Diabetes."

Association of Clinical Pathologists.—The 52nd general meeting will be held in Harrogate from April 8 to 10. Further information may be obtained from the honorary secretary of the association, Dr. W. H. McMenemey, Maida Vale Hospital for Nervous Diseases, London, W.9.

Institute of Biology.—A meeting is to be held on April 21 and 22 at the Royal Geographical Society, Kensington Gore, London, S.W.7, to discuss the training of biologists. A programme will be available from the general secretary, Institute of Biology, Tavistock House South, Tavistock Square, London, W.C.1.

Dartford Hospital Group.—A refresher course intended for general practitioners will be held at the Southern Hospital, Dartford, weekly on Fridays from 3.30 p.m. to 6 p.m. from April 23 until July 2. Further information may be obtained from Dr. J. C. Hogarth, Southern Hospital, Dartford.

Wessex Rahere Club.—The spring dinner will take place at the Royal Clarence Hotel, Exeter, on April 24. Mr. H. Jackson Burrows will be the guest of honour. Further details may be obtained from Mr. A. Daunt Bateman, 11, The Circus, Bath.

Seminar on World Health Organization.—The World Federation of United Nations is holding a seminar, for doctors, public health workers, and medical students, on the work of W.H.O., from May 3 to 15 at Geneva. Those attending the seminar will be able to go to the meetings of the seventh World Health Assembly, which is taking place at the same time, as well as to lectures and discussions led by senior W.H.O. officials. Further details may be obtained from W.F.U.N.A., 1, Avenue de la Paix, Geneva.

International Diabetes Federation.—The second congress will be held in Cambridge from July 4 to 8, 1955. Sir Lionel Whitby will be honorary president of the meeting.

NEW ISSUES

Thorax.—The next issue (Vol. 9, No. 1) will be available in a week's time. The contents include:

THE TREATMENT OF PULMONARY TUBERCULOSIS IN ADULTS BY RESECTION. H. T. Thompson, T. Savage, and T. H. L. Rosser.
THE PRODUCTION OF PLEURAL ADHESIONS BY KAOLIN INJECTION. James Maxwell.
EBSTEIN'S DISEASE. W. E. Medd, M. B. Matthews, and W. R. R. Thursfield.
NERVE SUPPLY TO THE CRURA OF THE DIAPHRAGM. J. Leigh Collis, L. M. Satchwell, and L. O. Abrams.
MALIGNANT CELLS IN SEROUS EFFUSIONS COMPLICATING BRONCHIAL CARCINOMA. Arthur I. Spriggs.
ENDOGENOUS LIPOID PNEUMONIA WITH SPECIAL REFERENCE TO CARCINOMA OF THE LUNG. S. De Navasquez and G. A. D. Haslewood.
AIR CONTAINING CYSTS OF LUNG. J. R. Belcher and A. H. M. Siddons.
PULMONARY MANIFESTATIONS IN THE DIFFUSE COLLAGEN DISEASES. Philip Ellman and L. Cudkowicz.
LINGULAR BIOPSY IN MITRAL STENOSIS. J. B. Enticknap, B. B. Milstein, and Charles Baker.
A CRITICAL DISCUSSION OF THE RECORDED FORM OF THE FAST VITAL CAPACITY RECORD. L. Bernstein.
UNILATERAL ELEVATION OF THE DIAPHRAGM IN DYSTROPHIA MYOTONICA. J. E. Caughey and W. G. Gray.
A CLINICAL, RADIOGRAPHIC, AND PATHOLOGICAL STUDY OF PULMONARY EMBOLISM. J. C. Macleod and I. W. B. Grant.
INSTRUMENTAL PERFORATION OF THE OESOPHAGUS AND PERFORATED DUODENAL ULCER James S. Davidson.
THE TREATMENT OF HYPERTROPHIC EMPHYSEMA BY PNEUMOPERITONEUM. Bertram Mann and Edmond A. Murphy.

Published quarterly; annual subscription £2 2s., single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Journal of Venereal Diseases.—The next issue (Vol. 30, No. 1) is now available.

Medical and Biological Illustration.—The next issue (Vol. 4, No. 1) will be available in a week's time.

Issued quarterly; annual subscription £2 2s.; single copy 12s. 6d.; obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, March 29

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor A. B. Nutt: Significance and Surgical Treatment of Congenital Ocular Palsies.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.15 p.m., Mr. Harold Edwards: Intestinal Diverticula.

Tuesday, March 30

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. R. French: Medico-Legal Problems and the Dermatologist.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. Harvey Jackson: Diagnosis and Treatment of Orbital Tumours; 6.30 p.m., Mr. C. P. Wilson: Malignant Disease of the Superior Maxilla.

●ROYAL SOCIETY OF ARTS.—5.15 p.m., Sir Arthur Porritt: Experiment of a State Medical Service in New Zealand.

ROYAL STATISTICAL SOCIETY: STUDY CIRCLE ON MEDICAL STATISTICS.—At Westminster Medical School, 6 p.m., Mr. N. T. J. Bailey: Queueing for Medical Care.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., neuroradiological demonstration by Dr. D. Gordon.

Wednesday, March 31

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Cytodiagnosis in Dermatology.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. G. F. Rowbotham: Surgical Aspects of Injuries to the Head; 6.30 p.m., Professor A. M. Boyd: Claudication.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. W. E. Tucker: Injuries in Sport.

Thursday, April 1

FACULTY OF HOMOEOPATHY.—5 p.m., Dr. J. C. Mackillop: Some Aspects of Homoeopathic Case-taking.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.30 p.m., Otolaryngology Lecture by Mr. G. A. Mason: Diagnosis, Treatment, and Prognosis of Tumours of the Lung.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.30 p.m., Dr. Wilfrid G. Oakley: Diabetes in Surgery.

ST. JOHN'S HOSPITAL DERMATOLOGICAL SOCIETY.—5 p.m., Symposium: Photosensitivity. Speakers: Dr. W. N. Goldsmith, Professor C. Rimington, and Dr. A. D. Porter.

Friday, April 2

LEEDS AND WEST RIDING MEDICO-CHIRURGICAL SOCIETY.—Sir Francis Walshe, F.R.S.: Some Lessons Learned in Consulting Practice.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Professor T. Pomfret Kilner: Reparative Surgery in the Treatment of Complications following Radiation; 6.30 p.m., Professor J. Trueta: Osteoarthritis of the Hip.

●SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At King's College, Strand, W.C., 7 p.m., annual general meeting; 7.30 p.m., Dr. D. S. Morris: Chloramphenicol.

WHIPPS CROSS HOSPITAL MEDICAL SOCIETY.—8.30 p.m., Professor A. Wilson: Peculiar Prescriptions. Members of the South-west Essex Division, B.M.A., are invited.

Saturday, April 3

KENT PAEDIATRIC SOCIETY.—At Royal Star Hotel, Maidstone, 3 p.m., Sir William Hamilton Fyfe: Some Platitudes on Education.

MIDLAND TUBERCULOSIS SOCIETY.—Visit to St. Wulstan's Hospital, Malvern, Clinical meeting.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Happel.—On March 16, 1954, at Alton General Hospital, Alton, Hants, to Margaret, wife of Dr. John S. Happel, D.Obst.R.C.O.G., of Ropley, Alresford, Hants, a daughter—Susan Margaret.

DEATHS

Beane.—On March 5, 1954, at Moretonhampstead, Devon, Robert Leonard Beane, M.R.C.S., L.R.C.P., aged 87.

Cormack.—On February 27, 1954, at Nairobi, Kenya, Robert Pairman Cormack, O.B.E., M.B., Ch.B., D.T.M.&H., D.P.H., Brigadier (retired), R.A.M.C., late Senior Medical Officer, Colonial Medical Service, Kenya.

Cumming.—On March 3, 1954, at Springfield House, Sutton-on-Hull, East Yorks, John Cumming, M.B., C.M.

Farrant.—On March 3, 1954, at his home, Charles Farrant, D.S.O., T.D., M.R.C.S., L.R.C.P., of Boldre, Lymington, Hampshire.

Fraser.—On February 28, 1954, at Craigroyston, Strathpeffer, Ross-shire, John James Fraser, M.B., C.M., aged 87.

Gupta.—On January 31, 1954, Subodh Chandra Gupta, M.B., F.R.C.S.Ed., of Calcutta, India.

Hare.—On March 5, 1954, at Cheltenhem, Glos., Edward Christian Hare, M.R.C.S., L.R.C.P., D.P.H., Lieutenant-Colonel, I.M.S., retired, aged 90.

Jackson.—On February 28, 1954, at Feock, Cornwall, Gordon Alexander Jackson, M.B., B.Ch., Surgeon Lieutenant-Commander, R.N., retired, aged 72.

Lyon-Smith.—On February 28, 1954, at his home, Spaxton, Bridgwater, Somerset, George Lyon Lyon-Smith, M.B., M.R.C.P., aged 61.

McGlasson.—In February, 1954, John Thomas McGlasson, M.B., Ch.B., of Canonbie, Dumfriesshire.

Tims.—On March 4, 1954, at Eldon House Nursing Home, Lower Bourne, Farnham, Surrey, Henry William Marett Tims, O.B.E., M.D., aged 90.

Umney.—On March 3, 1954, at 9, The Knoll, Beckenham, Kent, William Francis Umney, M.D., aged 87.

White.—On March 2, 1954, at Merthyr Vale, Glamorgan, Charles Richardson White, D.S.O., T.D., M.D.

Yealland.—On March 2, 1954, at 103, Clarence Gate Gardens, London, N.W., Louis Ralph Yealland, M.D., F.R.C.P.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Bodies for Dissection

Q.—*A patient wishes to leave his body for dissection, and has asked my advice on what steps he must take to do this. How should I answer him?*

A.—Strictly speaking no one can bequeath his own body, for as soon as he dies the legal right to dispose of it passes to his next-of-kin or the executor of his will. The body can be sent to a medical school for anatomical dissection only if the near relatives agree. Accordingly, if your patient wishes his body to be used for this purpose he should: (*a*) Ascertain that no objection will be raised by his nearest relatives. (*b*) Place with his papers a written statement of his wish to benefit medical education in this way. (*c*) Apply for the necessary forms and instructions to H.M. Inspector of Anatomy, Anatomy Office, Ministry of Health, Savile Row, London, W.1.

All expenses connected with the removal and subsequent burial of the body are borne by the medical school concerned, but if anything more than the very simple funeral provided by the medical school is desired then the executor or next-of-kin is expected to meet the expenditure.

Screening Test for Anaemia

Q.—*What are the details of the copper sulphate test which is used by the Blood Transfusion Service as a screening test for anaemia? How reliable is it?*

A.—A range of solutions of copper sulphate are prepared as described by R. A. Phillips *et al.*,[1] each being of known specific gravity. These can then be used to estimate the specific gravity of plasma or whole blood in the following way.

A drop of the plasma or blood is dropped into the solution, where it becomes encased in a sac of copper proteinate. Its momentum carries it 1 to 2 cm. below the surface, but in about 5 seconds the momentum of the fall is lost and the drop then begins to rise, becomes stationary, or continues to fall. The gravity of the drop relative to that of the solution remains constant for another 10 to 15 seconds and during this time its behaviour is noted. If it is lighter than the standard it will rise, perhaps only a few millimetres, and may then sink immediately. If the drop remains stationary for a few seconds its gravity is the same as that of the test solution; if the drop is heavier, it continues to fall. From comparison of plasma specific gravities with protein concentration calculated from Kjeldahl analyses an equation can be derived which permits the determination of protein concentration in normal plasma with an error of less than 0.1 g. per 100 ml. plasma (D. D. Van Slyke *et al.*[2]). The difference between the specific gravities of whole blood and plasma can be used to calculate the blood haemoglobin concentration, and, if one assumes a normal plasma protein concentration, the specific gravity of whole blood can be used to measure the haemoglobin concentration. Van Slyke *et al.*,[3] using the latter method on blood from normal individuals and from subjects with anaemia due to iron deficiency or blood loss and comparing the results with those of a precise gasometric method of haemoglobin determination, observed an error of ±0.5 g. haemoglobin per 100 ml.

A screening test, using a copper sulphate solution of specific gravity 1.053, allows a separation of those with haemoglobin concentrations above 12.5 g. per 100 ml. of blood (that is, about 85% Haldane) from those with lower

concentrations. The accuracy of the method within the limits mentioned depends upon the close observance of certain points. The solution must be properly prepared. The surface film must be clean and free from fragments; occasionally a part of a drop of blood remains attached to the surface film and might interfere with the passage of subsequent drops. The drops must be free of even minute air bubbles, which would make them float. The solution must be allowed to reach room temperature before use; if the solutions are used while warming, convection currents may interfere with the determination. The difference in temperature between the copper sulphate and blood should not exceed 5° C.; however, the error caused by dropping blood immediately after collection from a syringe or capillary tube is very small, because when the drop enters the solution the drop approaches the temperature of the solution so rapidly that the effects of several degrees of initial difference are nearly eliminated. A volume of 100 ml. of the test solution should not be used for more than 50 determinations. The solution must not be allowed to evaporate, for obvious reasons.

The limits of accuracy of this test have also been the subject of a field investigation, the results of which correspond very closely to those of Van Slyke *et al.*, quoted above. It does, however, occasionally happen under field conditions that a few donors are rejected who have in fact concentrations of haemoglobin above the limiting values.

This test is used by transfusion services in many parts of the world and has proved to be a reliable method for rapid examination of large numbers of individuals. Those persons whose haemoglobin concentration is shown by the copper sulphate test to be in the region of, or below, the critical level are usually tested by another method.

REFERENCES

1 *J. biol. Chem.*, 1950, **183**, 305.
2 Ibid., 1950, **183**, 331.
3 Ibid., 1950, **183**, 349.

Treatment of Still's Disease

Q.—*In what way does the treatment of rheumatoid arthritis in children (Still's disease) differ from that of adults? Is hormone therapy particularly indicated in children?*

A.—The principles to be observed in treating children with rheumatoid arthritis are no different from those to be followed in adults, but there are many small differences in their application. The major factors in successful treatment of both children and adults are five in number: (1) care of general health, (2) relief of pain by suitable analgesics, (3) maintenance of muscle tone and joint movement by active and passive exercises preceded by heat, with assistance by the masseuse or in a therapeutic pool, (4) prevention of deformity by adequate splinting, and (5) the maintenance of function and morale by adequate employment.

Deformities occur very rapidly in children, and once knee contracture has developed it may take many years of orthopaedic endeavour to regain even limited function. It is most important, therefore, to avoid absolute immobilization, and even in patients who are running considerable fever we endeavour to control this with salicylates and keep the children up and moving about for at least a short time every day. During rest periods, splints are necessary.

There is no specific cure for rheumatoid arthritis either in children or in adults; salicylates in various forms, phenylbutazone, cortisone, hydrocortisone, and corticotrophin (A.C.T.H.) are all useful for diminishing pain and increasing function in conjunction with a regime planned along the lines outlined above. Hormone therapy will sometimes bring a child back to a point where he can lead a normal life and, less frequently, maintain him at that level for a long period of years. It is a little too early yet to know whether these results are better in the long run than those obtained with agents such as salicylates. Hormone therapy is particularly indicated in children who do not respond adequately to the usual regime or whose disease for some reason or the other has become more active, possibly as the result of an infection or trauma. In view of the slightly better prognosis in children compared with that in adults, it might be maintained that hormones are particularly useful in children.

Multiple Meibomian Cysts in Children

Q.—*A girl, aged 4½, since birth has had no less than eight Meibomian cysts removed from all four eyelids at various times. What can be done to prevent their formation?*

A.—Children do sometimes suffer from repeated Meibomian cysts. In some instances marginal blepharitis appears to predispose to these cysts. Therefore the lid margins should be kept clear of dried secretion. If no blepharitis can be detected, there is no method of successful prophylaxis, but spontaneous cessation is the rule, and the eyelids hardly ever show any lasting damage from the cysts.

NOTES AND COMMENTS

Pharaoh's Ants.—Mr. H. E. Cox (Infestation Control Division of the Ministry of Agriculture and Fisheries, Hook Rise, Tolworth, Surbiton, Surrey) writes: We were pleased to see the publicity given to the treatment of a hospital infestation of Pharaoh's ant (*Monomorium pharaonis* L.) with chlordane ("Any Questions?" February 20, p. 471). We are in full agreement with the information given in your answer. We hope it would not be out of place for us to suggest that it might be emphasized that not only is treatment with chlordane an efficient control of Pharaoh's ant, and also for cockroaches, which are a common infestation of hospitals, but that the use of chlordane is an easy process. It is only too likely that the attitude of hospitals to infestations of Pharaoh's ant in the past has been rather controlled by the difficulties of the treatments recommended, which, although effective, require poison baiting with a prebaiting technique. No doubt the staff responsible for carry-out treatments in the past found it a tiresome process, with the inevitable result. We are always ready to give advice, particularly in difficult cases.

Phenylbutazone and Pulmonary Tuberculosis.—Dr. W. S. WILSON (Huddersfield) writes: Your answer to this question states that there is no contraindication to therapy ("Any Questions?" February 20, p. 471). About a year ago you published a letter of mine relating to the possible toxic effect of this drug in tuberculosis.[1] The patient was given phenylbutazone for a severe ankylosing spondylitis; on investigation for the latter complaint, an old-standing "quiescent" tuberculosis of the lung was discovered. After about four to six weeks' treatment with phenylbutazone, there was an acute flare-up of the tuberculosis. Although absolute proof is lacking, it is difficult to ignore the clinical impression of phenylbutazone toxicity in this case.

REFERENCE

1 *British Medical Journal*, 1953, **1**, 1388.

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